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THE EFFECT OF TESTOSTERONE PROPIONATE ON CARCINOMA OF THE FEMALE BREAST WITH SOFT TISSUE METASTASES

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IN A PREVIOUS communication (1) we reported the results obtained with testosterone therapy in patients with osseous and soft tissue metastases from carcinoma of the breast. The subsequent progress of the group with osseous metastases has been presented elsewhere (3). The present communication gives the subsequent course of the patients with soft tissue disease and also reports a new series of six patients with soft tissue lesions treated with the androgen.

S.K., referred to as "Case 1" in the previous report, exhibited a marked regression of the disease in the breast, a disappearance of supraclavicular, cervical and axillary lymph nodes and of skin nodules after receiving 3150 milligrams of testosterone propionate over a period of about two months. She suffered a psychic disturbance two months later and was institutionalized for one month. No androgen therapy was administered during her stay at the institute. She lost 10 pounds during this interval.

Subsequently, the patient returned to the Memorial Hospital. Examination revealed a recrudescence of the breast lesion but no evidence of recurrence of the disease in the previously involved supraclavicular, cervical and axillary nodes. A biopsy of the breast lesion was reported as mammary carcinoma with no unusual cytologic changes.

For a month following her return to the clinic, 25 mg. of testosterone

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propionate were administered biweekly. The breast lesion remained unchanged and no other external manifestation of the disease appeared. There was, however, progressive cachexia. Roentgenograms taken at the end of this month failed to reveal evidence of metastasis to the chest, lumbar spine, or pelvis. Shortly thereafter the patient failed to return to the clinic. She died about nine months after the institution of the androgen therapy, presumably of carcinoma.

The three other patients with soft part disease, who were under treatment at the time of the preliminary report, revealed cytologic alterations in the neoplasm following androgen therapy. These comprised hydropic changes in the cytoplasm and pyknosis of the nuclei. None of these patients revealed any gross evidence of regression of the lesions. All have since died of the disease.

The remainder of this report describes a new group of six patients with soft tissue lesions treated with testosterone propionate. The androgen was administered parenterally. Monthly determinations of the serum calcium, chlorides, phosphorus, alkaline phosphatase, and protein were made in every case, as well as frequent blood counts and routine urinalyses.

Case 1. *M.G.* is a 39-year-old white woman who was first seen at the Memorial Hospital November 15, 1945. Examination revealed an ulcerating mass in the right breast, a large hard node in the right axilla, and bilateral supraclavicular nodes. A roentgenogram showed fluid in the left chest to the level of the fourth rib, and a pathological fracture of the ninth rib on the left. The lumbar spine and pelvis revealed no evidence of metastasis. Aspiration biopsy of the breast mass was reported as carcinoma. Her menses were normal.

From November 27, 1945, to January 5, 1946, the patient received 200 mg. of testosterone propionate triweekly for a total of 3200 mg. From January 10, 1946, to April 20, 1946, she received 25 mg. weekly for a grand total of 3550 mg. No other therapy was employed.

The breast mass gradually increased in size as did the area of ulceration. Serial biopsies failed to reveal any cytologic changes. Monthly roentgenologic studies of the chest revealed a slight increase in the amount of fluid. An examination May 29, 1946, revealed widespread areas of metastasis in the lumbar spine and pelvis. There were, however, no symptoms referable to these lesions.

This patient is the only one in the present group who failed to gain weight while receiving testosterone therapy. Her weight gradually decreased from 120 pounds at the time therapy was instituted to 87 pounds seven months later. The menses were absent during this interval but the chemical castration failed to exert a favorable influence on the disease. She attends the clinic regularly. She complains only of pain in the left chest.

Case 2. *M.B.* is a 56-year-old white woman. A radical mastectomy was performed at the Memorial Hospital in May, 1944, for infiltrating duct carcinoma grade 3 with metastases to the axillary lymph nodes. She received roentgen ray therapy postoperatively. The patient had passed through the menopause.

There was no evidence of disease until August, 1945. She then developed over the xiphoid process a mass which, on biopsy, was reported as carcinoma. Roentgenograms

of the chest and sternum failed to reveal any evidence of metastasis. From August 17, 1945, to October 13, 1945, she received 200 mg. of testosterone propionate biweekly for a total of 3000 mg. The mass increased in size. Therapy was continued with 25 mg. biweekly from October 20, 1945, until December 4, 1945, for an all-inclusive total of 3375 mg. Roentgenograms of the lumbar spine, pelvis, lungs, and sternum taken November 27, 1945, failed to reveal any evidence of metastasis.

The mass continued to increase in size. Radiation therapy was then administered followed by regression of the lesion. Later, the patient developed a metastatic lesion in the scalp. A roentgenogram of the skull made January 5, 1946, was negative for metastasis. There was at no time any significant change in the blood chemistry or urine. She was institutionalized for terminal care in February, 1946.

Case 3. *A.C.* is a 54-year-old white woman. She first noticed a mass in the left breast late in 1937 but did nothing about it. The breast gradually contracted during the following years. In 1944, it began to ulcerate.

Examination at the Memorial Hospital in August, 1945, revealed the left breast to be contracted almost flush with the chest wall. The nipple and areola were replaced by a fungating mass. There were enlarged nodes in the left axilla, left supraclavicular, and left infraclavicular regions. She had passed through the menopause.

From August 21, 1945, to October 13, 1945, she received 200 mg. of testosterone propionate biweekly for a total dose of 3200 mg. She then received 25 mg. biweekly until February 2, 1946, for a grand total of about 4000 mg.

Serial biopsies failed to reveal any histologic changes in the carcinoma and the mass continued to increase in size. Therefore, roentgen therapy was instituted on February 9, 1946. This was followed by a complete regression of the mass and the lymph nodes.

The patient is apparently in good condition ten months after her initial visit to the clinic. There are no signs of activity of the disease. Roentgenograms of the chest, lumbar spine, and pelvis are negative for evidence of metastasis. No significant changes in the chemical constituents of the blood or urine have been noted.

The three additional patients in this group were treated exclusively with daily injections of 200 mg. of testosterone propionate for periods of five to seven weeks.

Case 4. *M.T.* is a 52-year-old white woman. She received roentgenotherapy to the left breast for an inoperable carcinoma in February, 1945, at the Memorial Hospital. One year later she developed an inflammatory carcinoma in the previously irradiated breast. Biopsy revealed carcinoma invading the dermal lymphatics. She had passed through the menopause.

Beginning March 4, 1946, the patient received 200 mg. of testosterone propionate five days a week for seven weeks, for a total dose of 7000 mg. At the end of this period an atrophic vaginal smear was obtained, indicating a full androgenic effect. She has been under observation for two months since termination of the therapy. During this time the process has spread from the left breast onto the chest and shoulder and has appeared in the opposite breast. Serial biopsies have failed to reveal any cytologic changes. There have been no significant changes in the blood or urine.

Case 5. *G.U.* is a 40-year-old white woman. A left radical mastectomy was performed in May, 1945, at another institution. Examination in March, 1946, at the Memorial Hospital revealed a large area of superficial ulceration on the left chest wall. The surrounding skin was studded with metastatic nodules. There were enlarged supraclavicular

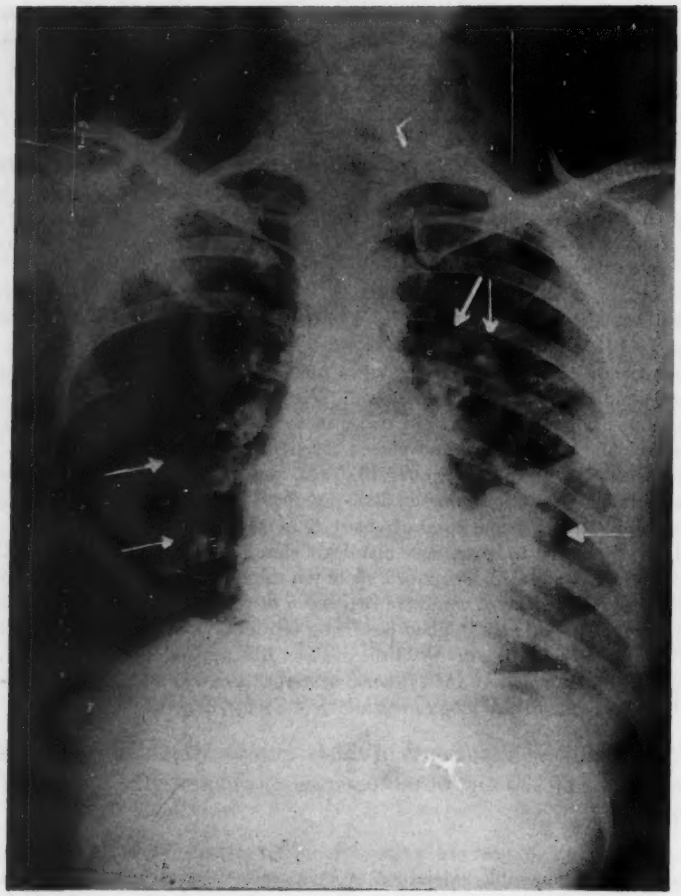

FIG. 1. Numerous areas of large and small metastases are scattered throughout both lung fields. The metastases are nodular in type and show some confluency on the left side.

and cervical lymph nodes. A biopsy of a cutaneous nodule was reported as mammary carcinoma invading the skin. Roentgenograms of the chest, lumbar spine, and pelvis failed to reveal evidence of metastasis. Her menstrual periods were regular.

Beginning March 23, 1945, the patient received 200 mg. of testosterone propionate six days a week for five weeks, for a total dose of 6000 mg. A vaginal smear taken at this time revealed the atrophic picture characteristic of a full androgenic effect.

She had a menstrual period March 10, 1945, about two weeks before the androgen therapy was instituted, and another period April 2, 1945, after ten days of therapy. She skipped the period which should have appeared April 30, 1945. On May 28, 1946, one month after withdrawal of the androgen, she had a period of two days' duration.

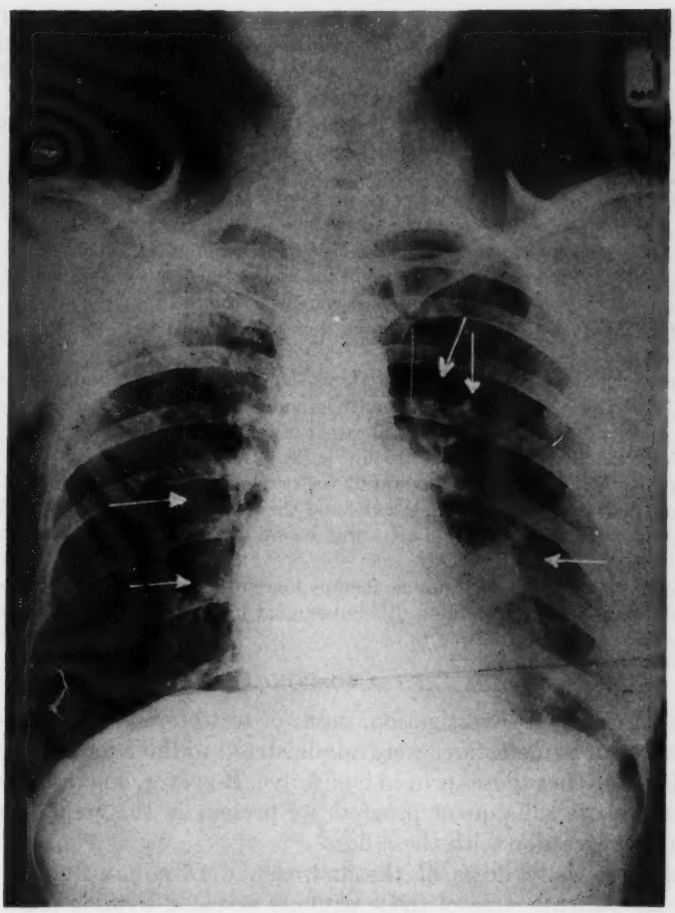

FIG. 2. This roentgenogram was made nine weeks after the preceding one. In the interim the patient had received 6400 mg. of testosterone propionate. The metastases in both lung fields have diminished in size and number.

During the period of androgen administration, the patient gained 15 pounds. She has been under observation for two months since cessation of therapy and has lost 8 pounds. There has been no evidence of clinical improvement. Serial biopsies have revealed no cytologic changes. No significant changes have been noted in the blood or urine at any time.

Case 6. *I.S.* is a 27-year-old white woman. A right radical mastectomy was performed in March, 1944, at the Memorial Hospital. The pathologic finding was infiltrating duct carcinoma grade 3 with metastases to the axillary lymph nodes. She received roentgen ray therapy postoperatively to the right axilla. Her menses were regular.

She was apparently free of disease until February, 1946. Examination at this time revealed several firm nodes 1 cm. in diameter at the inner part of the left supraclavicular space. An aspiration biopsy of one of these nodes was reported as carcinoma. She complained of cough and hemoptysis. Roentgenograms taken February 18, 1946, revealed evidence of numerous small and large metastases in both lungs but no evidence of disease in the lumbar spine and pelvis (Fig. 1).

Beginning March 9, 1946, for a period of six weeks, the patient received 200 mg. of testosterone propionate five days a week for a total dose of 6400 mg. At this point the therapy was stopped because of pain and swelling in the legs. A vaginal smear revealed the atrophic cytology characteristic of a full androgenic effect. The pretibial edema gradually subsided following withdrawal of the androgen. About one month after institution of the therapy the patient no longer coughed. Examination on April 20, 1946, six weeks after institution of the testosterone therapy, revealed that the supraclavicular nodes were no longer palpable.

A roentgenogram of the chest made March 30, 1946, revealed a slight diminution in the size of the previously described multiple nodular cancer metastases in both lung fields. A further decrease in the size and extent of the pulmonary metastases was noted in radiologic studies made May 23, 1946 (Fig. 2).

The patient has been under observation for two months since the androgen therapy has been withdrawn. She is asymptomatic and there is no external evidence of disease. She skipped one menstrual period after withdrawal of the androgen. The menses then returned.

During the six weeks of testosterone therapy there was a gain of 18 pounds, which was probably due to nitrogen retention (2). Subsequent to the withdrawal of the androgen there was a loss of 10 pounds.

SUMMARY AND CONCLUSIONS

1. In the present investigation, doses of testosterone propionate which influence osseous metastases were administered to three patients with soft tissue lesions. These doses proved ineffective. However, one case previously reported, whose subsequent progress we present in this paper, did show temporary regression with these doses.

2. Massive daily doses of the androgen were administered to three additional patients. One of these patients revealed striking regression of the lesions.

3. The administration of large amounts of androgen apparently had no effect on the subsequent response of lesions to roentgen therapy.

4. Despite the administration of massive doses of the androgen, the menses were suppressed for only one period following withdrawal of the androgen.

5. Suppression of the menses in one patient for seven months by the continued administration of the androgen did not influence the soft tissue lesions.

6. During the time testosterone propionate was administered, in every patient, except one, there was an increase in weight which was lost subsequent to the withdrawal of the androgen.

7. Facial hirsutism, deepening of the voice, acne, and an increase in libido were encountered to a greater or less degree in all of the patients.

ACKNOWLEDGMENT

The authors wish to thank Dr. Anne C. Carter of the Department of Endocrinology, Cornell Medical School, for interpreting the vaginal smears. We are also indebted to the Schering Corporation of Bloomfield, N. J., for furnishing us with the testosterone propionate (Oreton) used in this investigation.

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CRANIOPHARYNGIOMA WITH PANHYPOPITUITARISM: CASE REPORT WITH CLINICAL AND PATHOLOGICAL STUDY*

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LONG-TERM clinical observations of glandular deficiencies in the human being afford one of the best means of determining the effects of each of the glands involved. In the present instance, the clinical course of a man with craniopharyngioma and hypopituitarism was followed for five years, during periods without treatment as well as at times when the effects of various glandular preparations were recorded. The unusual nature of some of these results, especially in regard to water and electrolyte[1] balance, and the opportunity to study the postmortem data, have prompted this report.

CASE REPORT

P.B., an Italian by birth, died January 21, 1946, at the age of 55 years, following repeated admissions to the Metropolitan and other New York City hospitals for apparently minor but distressing low-grade infections associated with progressive weakness, and ease of fatigue on the slightest exertion. He had not been well since the age of 14 years, when he developed polyuria, polydipsia, and generalized constant headaches with a sense of pressure. The first two of these symptoms were extreme in degree and persisted until the age of 17, when they disappeared completely. More or less continuous headache persisted until the age of 21, with occasional mild recurrences ever since.

His familial history was noncontributory. His birth was normal, and early childhood uneventful.

His general development ceased about the age of 13, and growth stopped between the ages of 15 and 17 years. His voice was high-pitched, his skin soft and almost completely devoid of hair, even in the axillae and about the genitalia. Libido and potency had never been present save for a short period of time about the age of 30 years. He had never had to shave more often than once monthly. His mentality was unimpaired. His appetite was always poor, but "digestion good." He was "never strong," but was able to make a living at light work until the age of 46 when his weakness, tiredness, and marked tendency to develop low-grade infections of the nose, throat, and eyes more or less com-

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[1] The water and electrolyte studies were made possible through therapeutic grants #509 and #538 from the Council on Pharmacy and Chemistry, American Medical Association.

pletely incapacitated him. From this time until his death nine years later, he was subject to periods of mental as well as physical depression. When first admitted to the Metropolitan Hospital at the age of 49, he had lost 15 to 20 pounds, and complained bitterly of coldness, of dizziness, and of "narrowed" vision.

Physical examination at that time revealed an intelligent, cooperative, pale, pasty-faced, soft-skinned, slightly undernourished individual of eunuchoid habitus and mongoloid facies. His height was 64.8 inches, his span 70 inches, and his lower measurement 38.8 inches. His weight was 106 pounds and his blood pressure 120/65. His voice was high-pitched and harsh. The hair of the scalp was well preserved, but dry. The hair of the eyebrows and about the genitals was scanty; only lanugo hair was present over other parts of the body. The forehead was somewhat receding; the ears, large and pointed. A slight feminine flare of the pelvis was noted. The arms and legs were long. The hands and feet were large and the fingers long and tapering. There was a generalized muscular atonia. Perimetric examination of the visual fields showed only a slight defect in the upper outer quadrant. The vision was 20/20 in the right eye, and 20/30 in the left. The optic discs were pale, but no other abnormalities were observed on examination of the fundus. The tongue was slightly enlarged. There was a low-grade chronic granular pharyngitis. The vocal cords were short and the larynx "infantile." The genitals were hypoplastic. The dorsal length of the flaccid penis was 7.5 cm. Each of the testes was soft and about the size of a pea. The prostate was outlined with difficulty on digital rectal examination; no secretion could be expressed from it. A specimen obtained later, following masturbation, showed complete azoospermia.

On admission, urinalysis was essentially negative. The hemoglobin was 74 per cent. There were 3.76 million red cells per cu. mm. and 8.85 thousand white blood cells per cu. mm. A differential leucocyte count revealed the following percentages of various cells: polymorphonuclear neutrophils, 51; lymphocytes, 41; monocytes, 1; and eosinophils, 7. Repeated counts throughout his various hospitalizations always showed the same moderate secondary anemia; the white count responded characteristically to infection, but at other times closely resembled that just recorded.

The icteric index was 5.6. The blood Wassermann was negative. The rate of sedimentation of erythrocytes (Westergren method) was 4 mm. in fifteen minutes, and 20 mm. in one hour. The van den Bergh and cephalin flocculation reactions were negative. The alkaline phosphatase of the serum was 5.0 Bodansky units. The total serum protein was 6.40 per cent with an albumin-globulin ratio of 1.88. Other blood chemical constituents in mg. per 100 cc. were: total cholesterol, 240; free cholesterol, 88; total nonprotein nitrogen, 30.0; urea nitrogen, 12.5; creatinine, 1.1; creatine, 0.153; glucose, 70; sodium, 330; potassium, 18; chloride (as NaCl), 605. His basal metabolic rate was minus 24.

Roentgenograms of the skull revealed an enlargement of the sella turcica with an anteroposterior diameter of 22 mm. and a depth of 10 mm. (Fig. 1). The floor of the fossa, and both the anterior and posterior clinoid processes were partially destroyed. A nonhomogeneous, irregularly-shaped area of calcification was observed within the sella. Roentgenograms of all four extremities revealed a line of increased density at the points corresponding to the previously located epiphysial lines. The pelvis was android in type. The cardiac shadow was small.

In the electrocardiographic tracing, the PR interval varied from 0.20 to 0.23 seconds. T-1 was low; T-2 was inverted.

The patient's progress during the last five years of life was intimately connected with a study of the influences of various hormonal factors upon his clinical condition.

The majority of this data is summarized in tables 1 and 2, and figures 1 to 7 inclusive. All of the laboratory analyses mentioned above, and a number of others, were frequently repeated, but will be discussed in relation to the hormonal studies only if affected thereby. The patient's weakness was slowly progressive, except for periods of improvement attained by testosterone preparations, desiccated thyrcid substance, and combinations of the two. Frequent sore throats, two frank attacks of acute follicular tonsillitis, several attacks of iridocyclitis, mild furunculosis, three attacks of bronchitis, and two episodes of generalized urticaria punctuated an otherwise slowly-downhill course, in which weak-

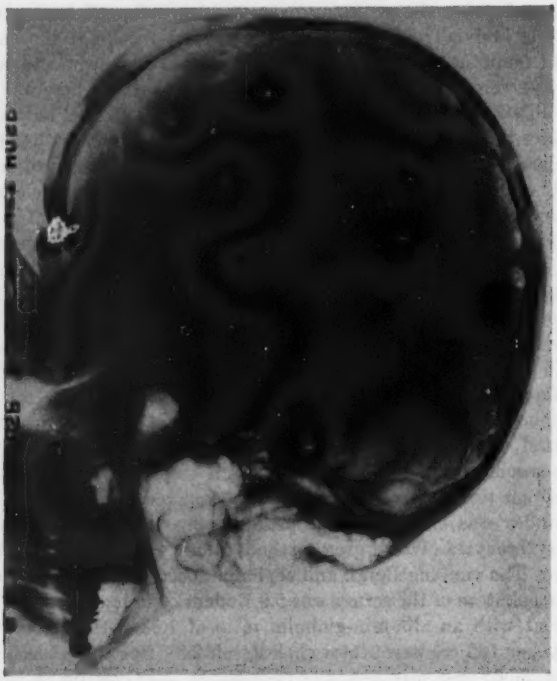

FIG. 1. Roentgenogram of the sella turcica. The anteroposterior diameter is approximately 22 mm. and the depth 10 mm. Note the erosion of the clinoid processes and the floor of the sella. Shadows of calcium are visible throughout the intrasellar space.

ness, anorexia, and an increasing susceptibility to infection were outstanding features. Effort was made to improve anorexia with a small dose of insulin, five units before each meal. Following the second dose, the patient became stuporous, his blood pressure dropped from 130/70 to 100/60, and some spasticity of the left arm, a bilateral Babinski, Cheyne-Stokes type of respiration, and mild tetanic spasms of the face, arms, and hands were noted. The blood glucose at that time was 55; while his hypoglycemia was promptly relieved, he died about sixty hours later without fully recovering from the secondary effects of the hypoglycemic episode.

SUMMARY OF SIGNIFICANT POSTMORTEM FINDINGS

There was a congestion and edema of the lungs; the right weighed 665 gm. and the left, 550 gm. The heart weighed 365 gm. The coronary arteries were sclerotic; atheromatous plaques were present on the auricular surface of the mitral valve. The spleen weighed 160 gm., the liver, 1560 gm. and the pancreas, 49.1 gm. Grossly there was evidence of an increase in connective tissue in the pancreas; this was confirmed on microscopic examination. The right and left kidneys weighed 140 and 135 gm., respectively, and showed only a marked congestion. The brain, with the contents of the sella turcica attached, weighed 1437 gm. and was grossly normal except for the neoplastic mass attached to it in the region of the pituitary.

No normal pituitary tissue could be identified grossly. The very firm,

TABLE 1

P.B.—WEIGHT OR SIZE OF ENDOCRINE ORGANS
(gm. or cm.)

Pituitary and Tumor	4×4×3
Thyroid and Parathyroids	9.7
Pancreas	49.1
Adrenal—right	3.6
—left	3.3
Testis —right	3.6
—left plus implant	4.4
Prostate	10.2

partly calcified, irregularly globular mass which replaced it measured 4×4×3 cm. (Table 1). Microscopic examination revealed that both the pars glandularis and the pars nervosa were almost completely destroyed. A small rim of glandular tissue was compressed by the calcified cystic tumor (Fig. 2a and 2b). About 90 per cent of the cells in this area were eosinophilic, approximately 10 per cent, chromophobic, and a few, basophilic in type. The tumor itself was mainly a mass of fibrous tissue infiltrated with calcium salts. It contained cystic areas of varying size, for which no lining epithelial membrane could be identified.

The thyroid and parathyroid glands (Fig. 2c) together weighed 9.7 gm. On section, relatively large, greyish-white strands were observed against the purplish parenchymal background of the thyroid. The marked increase in connective tissue was confirmed microscopically. In many areas it was highly cellular. Many of the acini were filled with colloid and lined with flat epithelial cells. The parathyroids were small, but appeared grossly and microscopically normal.

The right and left adrenals weighed 3.6 and 3.3 gm., respectively. In each, there was an almost complete disappearance of the adrenal medulla. Despite the occasional presence in the cortex of very small hyperplastic nodules, the entire structure was markedly atrophic and its architecture completely disorganized (Fig. 2d and 2e). In some instances, the aggregations of cells appeared as irregularly broken rows, and in others, they

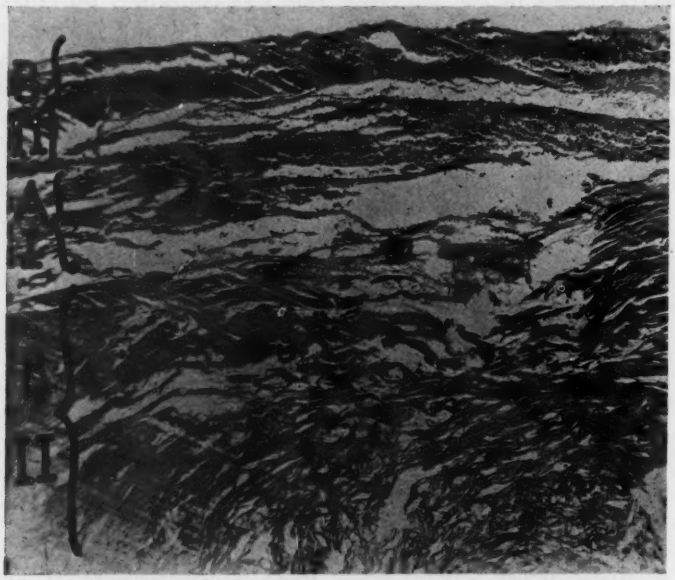

FIG. 2a. Pituitary and pituitary tumor (approximately ×40).

I. Narrow strip of normal pituitary cells, consisting of eosinophilic forms, approximately 90 per cent, chromophobic types, approximately 10 per cent, and a few scattered basophilic elements.

II. Tumor tissue.

tended to form rosettes. Such groups of cells were widely separated by broad strands of fibrous tissue. The cells themselves were small, deeply staining, and frequently showed bizarre nuclear formations.

The right and left testis weighed 2.8 and 4.4 gm., respectively; the latter included the remnants of three pellets of testosterone which weighed 65. mg. The normal seminiferous tubular structure was replaced by numerous "ghost tubules" (Fig. 2f). These were rather acellular and lined by a single layer of flat epithelial cells. All evidence of spermatogenesis was lost. The epididymis showed some normal tubules containing amorphous material and mononuclear cells. Surrounding the tubules there was an

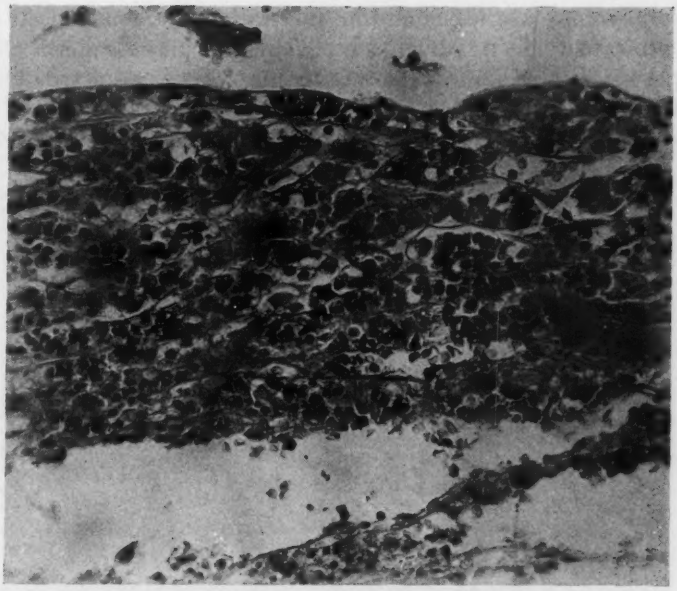

FIG. 2b. Pituitary and pituitary tumor (approximately ×890). Higher power of 2a, I and II, showing arrangement and types of cells.

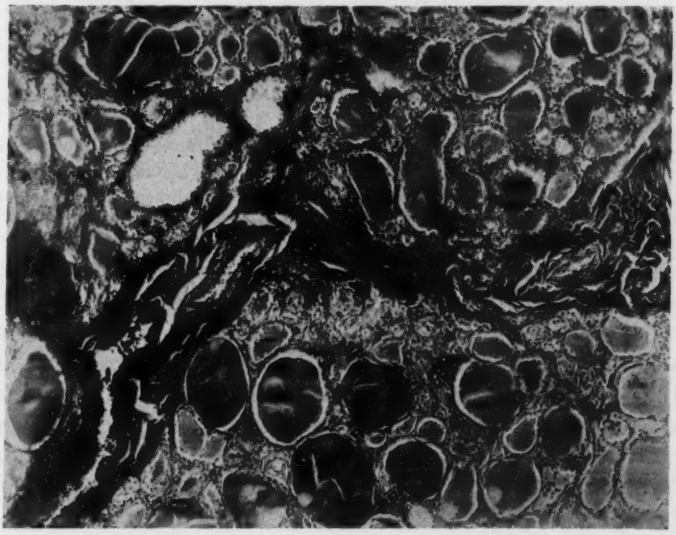

FIG. 2c. The thyroid (approximately ×130). Note the marked increase in interacinar collagenous and fibrous tissue and the very flat follicular epithelium.

increase in connective tissue and an infiltration by mononuclear cells.

The prostate weighed 10.2 gm. and, on microscopic examination, showed a comparatively normal architecture with a tendency towards glandular hyperplasia.

Diagnosis: Intrasellar type of craniopharyngioma with compression and

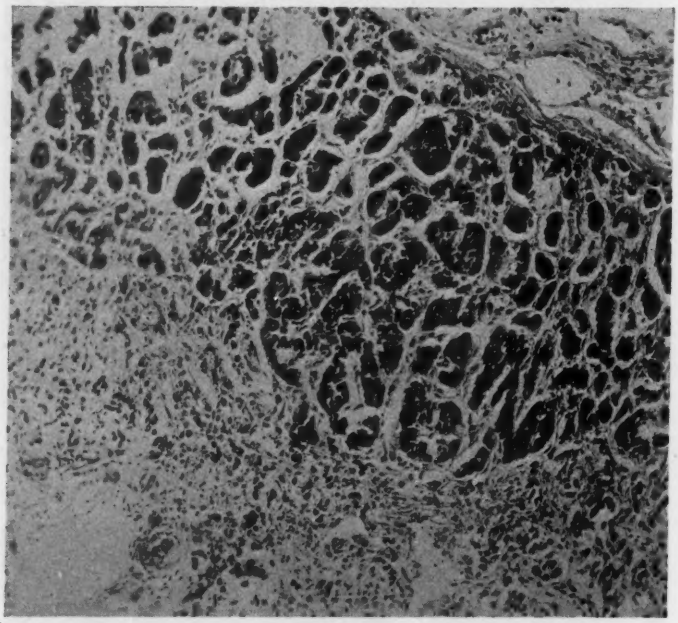

FIG. 2d. The adrenals (approximately ×140). The adrenals are almost entirely bordered by moderately heavy strands of fibrous tissue, which extend into and between the broken rows of cortical cells. The zonal arrangement of the cortex is completely lost. In many sections no evidence of the medullary tissue was observed.

destruction of the pituitary gland; secondary atrophy of the thyroid, adrenals, testes, and prostate; pulmonary edema and congestion.

PROCEDURES AND TECHNICS

During the last two and a half years of his life, and throughout all periods during which data were collected, the patient was maintained on a diet of 2040 calories, which was supplied by 250 gm. of carbohydrate, 90 gm. of protein, and 80 gm. of fat. The sodium of the diet was always measured and was maintained at 2.6 gm. daily for the majority of the observations and at 4.5 gm. for the remainder. Potassium in the diet varied from 3.2 to 4.0 gm. daily.

Methyl testosterone was given by mouth, 100 mg. daily. Testosterone propionate was given intramuscularly in doses ranging from 50 mg. daily to 25 mg. once weekly. Crystalline testosterone was implanted intratesticularly in the form of 75 mg. pellets in total amounts varying from 75

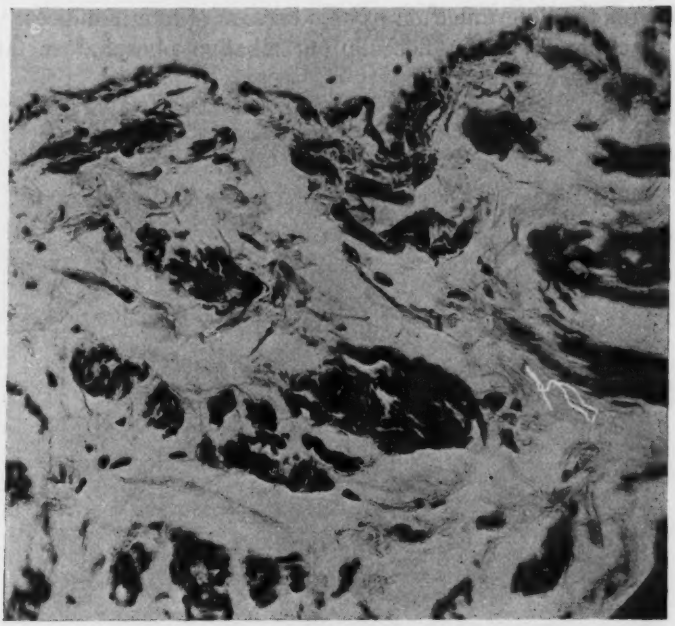

FIG. 2e. The adrenals (approximately ×600); a higher magnification to show the relatively small size of the cells, the absence of normal architecture and the high degree of atrophy and fibrosis.

to 225 mg. Desoxycorticosterone acetate was administered intramuscularly as a solution in sesame oil and in doses of 10 and 15 mg. daily, respectively. Alpha-estradiol dipropionate was injected intramuscularly as a solution in sesame oil, 1 mg. per daily dose. Three doses of prolactin, each consisting of 1 cc. were given daily.*

Each of the above hormones was used over relatively long periods of time and for more than one experimental period. Control periods were of sufficiently long duration to permit all of the effects of the agent to dis-

* The methyl testosterone and testosterone propionate used in these studies were furnished through the courtesy of Dr. Leo Pirk of Roche-Organon, Inc. The prolactin, the testosterone pellets, the desoxycorticosterone acetate, and all of the alpha-estradiol dipropionate were kindly supplied through the courtesy of Dr. Leon Henderson of the Schering Corporation.

appear, as shown by the clinical condition of the subject and the results of laboratory procedures. Through repetition of the studies with each hormone, many extrinsic factors, such as the time of the year, variations due to available dietary materials, and so forth, were minimized.

The composite liver function test described by Schwimmer *et al.* (24) was used for the determination in blood serum of icteric indices, van den Bergh reactions, cephalin flocculation, alkaline phosphatase, albumin,

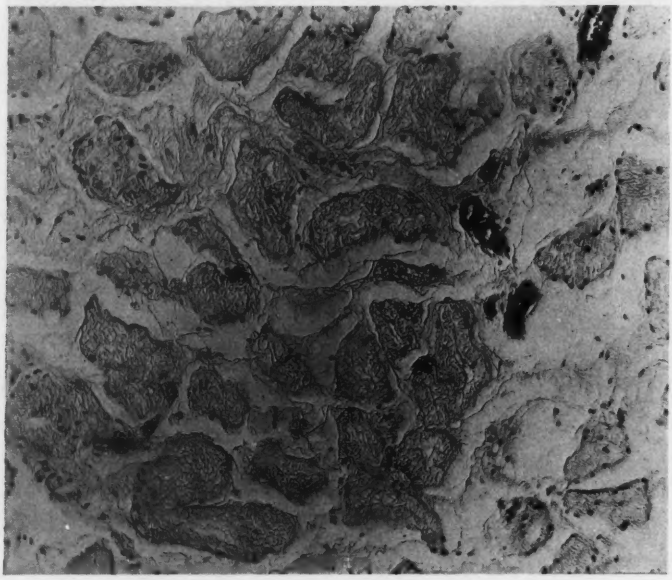

FIG. 2f. The testis (approximately ×130). Note the relatively acellular ghost tubules, devoid of any resemblance to the normal seminiferous tubule.

globulin, cholesterol and cholesterol esters. The determination of sodium in the blood and urine was made by the method of Darnell and Walker (6); that of potassium in the same fluids by the procedure of Drekter (8). Chlorides were estimated by the method of Wilson and Ball (31). Inulin clearances were carried out according to the technic devised by Alving and Miller (1). Capillary permeability and circulation times were determined by the procedure of Lange and Boyd (17). Creatine and creatinine of the blood and urine were estimated by the methods described by Folin (10). Glucose tolerance tests were performed according to the procedure of Thorn *et al.* (30), slightly adapted to our facility (22). The area of the control curves was calculated and arbitrarily fixed at 100 per cent. Test curves

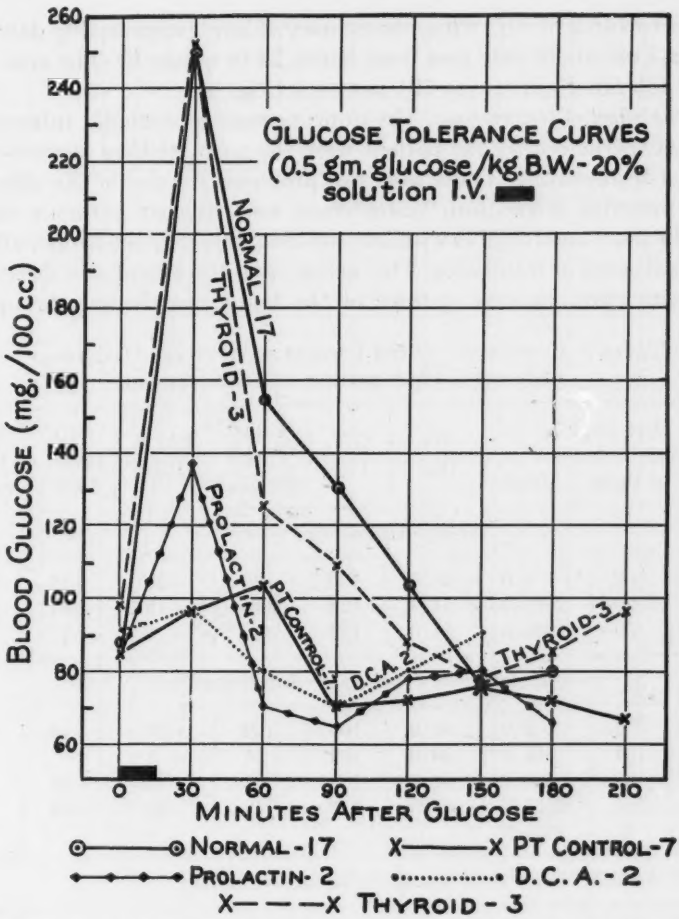

FIG. 3. Numerals on the curves following names represent the number of determinations on which the composite curve is based.

were similarly calculated and reported as a percentage figure of the control.

Kepler and Robinson water tests followed the originally described technic (15). Basal metabolic rates were recorded on a portable graphic metabolor.

RESULTS

A. *The effect of Riddle's prolactin.* Three cc. of Riddle's prolactin were used daily for thirteen days. During this period the patient's weight increased from 50.4 to 51.8 kg. The serum sodium rose from 131.7 m. eq.

per liter to 145.2 m. eq., while the urinary chloride appreciably decreased. The basal metabolic rate rose from minus 24 to minus 12. The area of the glucose tolerance curve was 121 per cent (Fig. 3).

B. *The effect of testosterone.* The improvement in strength, interest, and activity experienced by the patient were the most striking features of the action of testosterone. These were not produced by any of the other hormonal material used. Both testosterone and thyroid hormone enabled him to be more comfortable with less clothing, but only the former afforded him a real sense of well-being. This action, and the extent and direction of the effects upon various systems of the body as reflected through the

TABLE 2. COMPARISON OF THE EFFECTS IN PITUITARY DEFICIENCY OF SEVERAL PREPARATIONS OF TESTOSTERONE

Dose (mg)			Wt. (kg)	G.T. (%)	Urine Ctne. (mg./da.)	B.M.R. (%)	Cap. Perm. (%)	Inulin Clear. cc./mm.
Daily	# Days	Total						
Methyl Testosterone—Orally								
0.0	0	0.0	48.9	100	129	−24	+45	70
100.0	20	2000.0	51.4	123	144	−10	−34	119
100.0	30	3000.0	51.0	153	332	− 1	−10	
Testosterone Propionate—Intramuscularly								
0.0	0	0.0	45.9	100	129	−24	+45	70
25.0	34	850.0	50.9	130	26	+ 4		82
25.0	60	1500.0	54.5	158	23	+ 4	−22	102
25.0	101	2525.0	53.6	116	40	−22	+22	
7.1	41	2825.0						
Testosterone Propionate—Implant								
0.0	0	0.0	53.6	100	129	−24	+45	70
0.7	7	4.9	53.6	168		− 9	− 3	
0.7	31	21.7	53.6	172	50	+ 7	−30	110
2.1	30	63.0	53.7	100	33	−11	0	
2.1	52	109.2	54.1	130	30	−20	+ 1	58

results of laboratory procedures, were dependent upon a number of factors —among other things, upon the preparation employed, its method of administration, and the size of the dose.

1. **Testosterone propionate and testosterone.** The quality of the activity of these preparations was the same (Table 2), but the effective daily absorption of the latter from intratesticular implants was approximately one-thirtieth of the former when given intra-

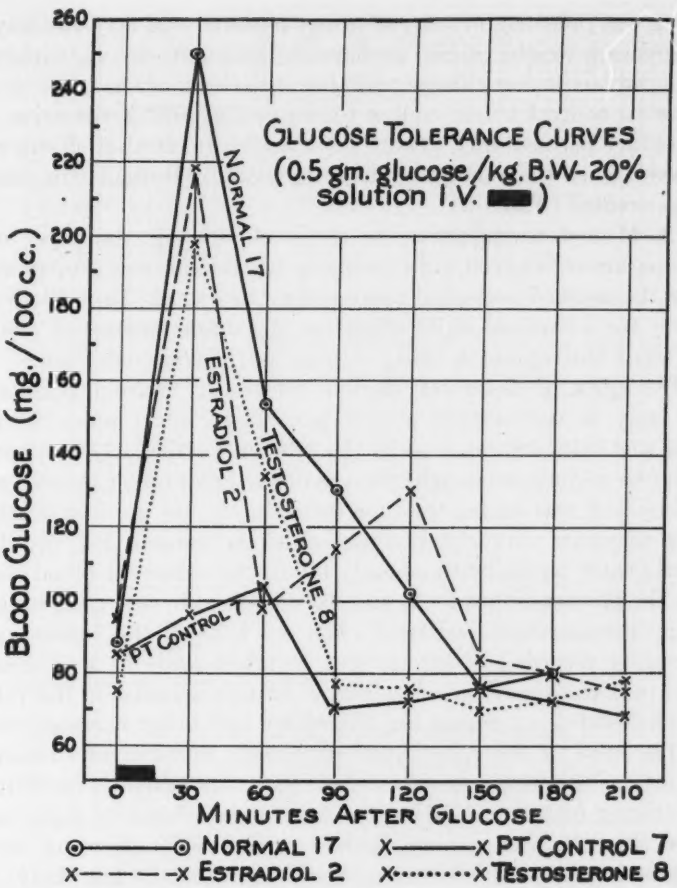

FIG. 4. Numerals on the curves following names have the same significance as in Fig. 3.

muscularly (Table 2). A phasic action of these two preparations, dependent upon dose and period of time over which used, was apparent not only in the subjective symptoms of the patient but also in the laboratory data obtained.

For the first sixty days, a daily intramuscular dose of 25 mg. of testosterone propionate caused a steady, rather rapid gain in weight, an improvement in glucose tolerance towards the normal (Table 2 and Fig. 4), a sharp and sustained decrease in creatinuria, an increase to normal in the basal metabolic rate, a decrease in capillary permeability, and a return of the inulin clearance to normal. A tendency for these effects to be reversed following the long-continued use of the

drug was reflected, at the end of one hundred and fifty-two days, in a decreasing weight, slight, perhaps insignificant, rise in urinary creatine, an increase in glucose tolerance, a decrease of the basal metabolic rate to control levels, and a tendency for similar reversion in the capillary permeability (Table 2). A similar reversal of effects was observed when the amount of the drug given by testicular implantation was trebled (Table 2).

2. **Methyl testosterone.** In doses of 100 mg. daily per os, this preparation behaved very similarly to testosterone propionate save for the marked sustained creatinuria it produced (Table 2). No tendency for a reversal of its effects in the doses mentioned above was evident throughout a thirty-day period of administration.

C. *The effect of desiccated thyroid substance.* Thyroid hormone was second only to testosterone preparations in its effect upon the general sense of well-being experienced by the subject. Particularly noticeable was the relief of coldness although this was not as great under thyroid medication alone as it was during the time testosterone was simultaneously used. Glucose tolerance very closely approached the normal (Fig. 3), although there was some tendency to an early fall in the values for blood sugar following the glucose infusion. As the basal metabolic rate rose, weight and capillary permeability decreased (Fig. 5). Indeed, the lowest capillary permeability recorded in this patient occurred while he was receiving a thyroid preparation. Thyroid caused a definite decrease in the values for blood cholesterol, an action not shared by any other hormone tried.

D. *The effect of desoxycorticosterone acetate.* Subjectively, desoxycorticosterone acetate had little or no effect upon the patient's condition. The most striking features of its entire action were related to water and salt balance (Fig. 6). The urinary volume trebled while the drug was being used. Despite the relatively low intake of sodium (2.56 gm. daily), a positive balance for this substance, associated with a gain in weight, was promptly established by the use of 10 mg. of desoxycorticosterone acetate daily. Despite its continued use, a negative balance occurred about the thirtieth day, accompanied by a definite decrease in weight and a slight decrease in the already high urinary volume. An addition of 5 mg. of desoxycorticosterone acetate to the daily dose, making a total of 15 mg. daily, again produced a marked retention of sodium with a gain in weight. On this occasion, however, the value for sodium in the blood serum, which had not been previously disturbed, increased to 192.1 m. eq. per liter. While the blood sodium remained high and the urinary excretion low, potassium behaved in an exactly opposite manner. A prolonged period of sodium excretion followed the period of sodium retention, during the first

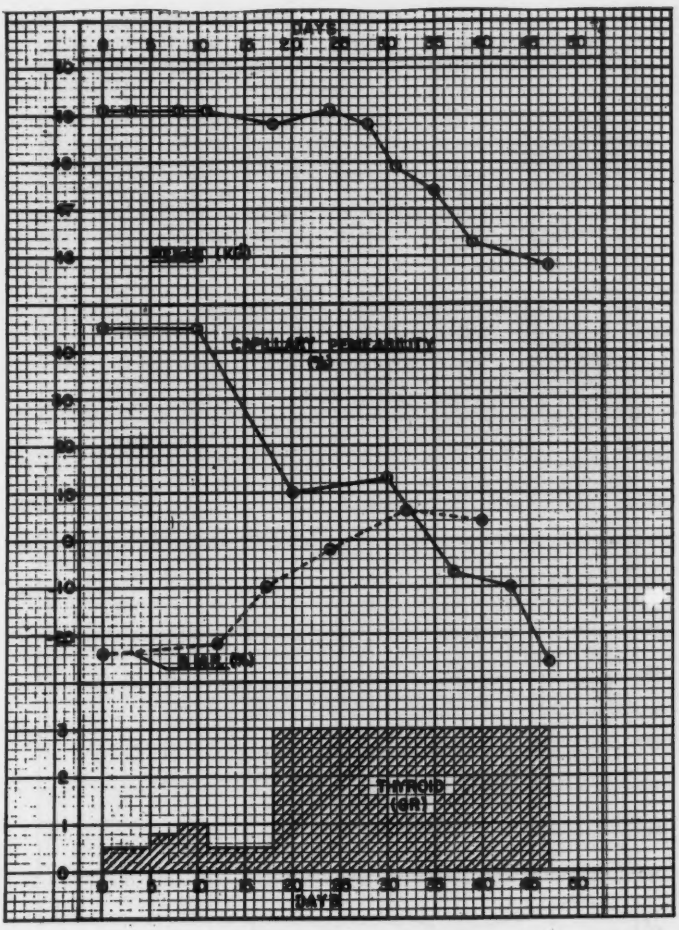

FIG. 5

portion of which the urinary volume reached its highest level: 3200 cc. daily (Fig. 6).

The negative balance for sodium continued for ten days after desoxycorticosterone acetate was stopped, during which time the urinary volume also remained high. Before a positive balance was reestablished on the eleventh day, the sodium of the serum had dropped to 131.3 m. eq. per liter, and the weight to 48.4 kg. as contrasted with 50.0 kg. at the time the administration of desoxycorticosterone acetate was begun.

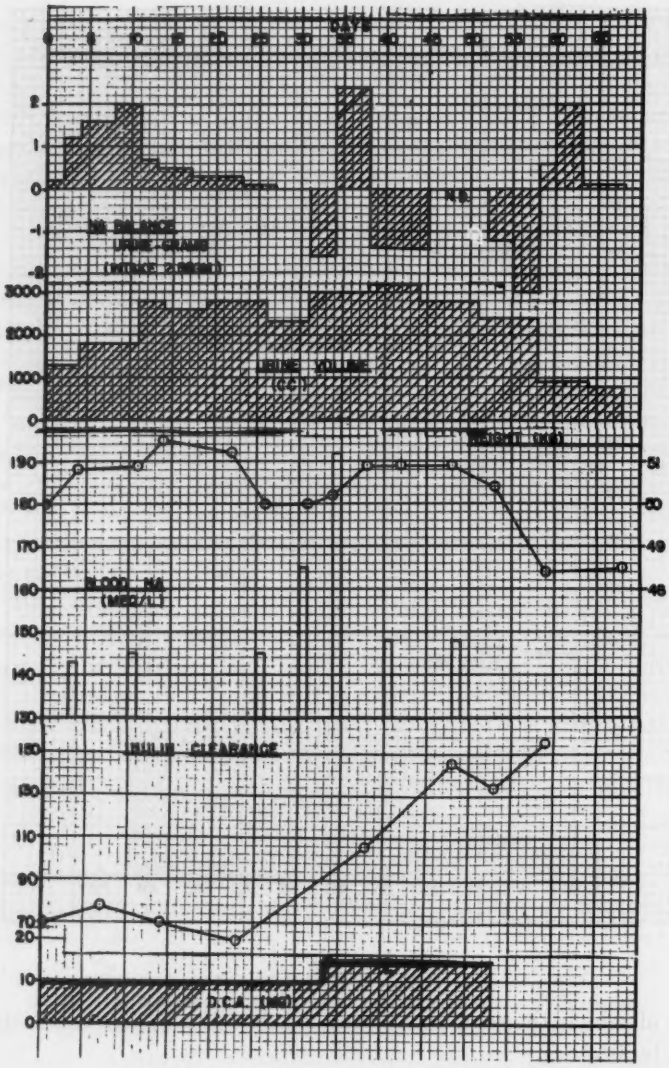

FIG. 6

The basal metabolic rate rose to minus 7 per cent on the thirty-eighth day of treatment with desoxycorticosterone acetate, but was back to control levels eleven days after the drug was discontinued. Inulin clearance remained low until the second period of diuresis began, following an increase in the dose of desoxycorticosterone acetate from 10 to 15 mg.

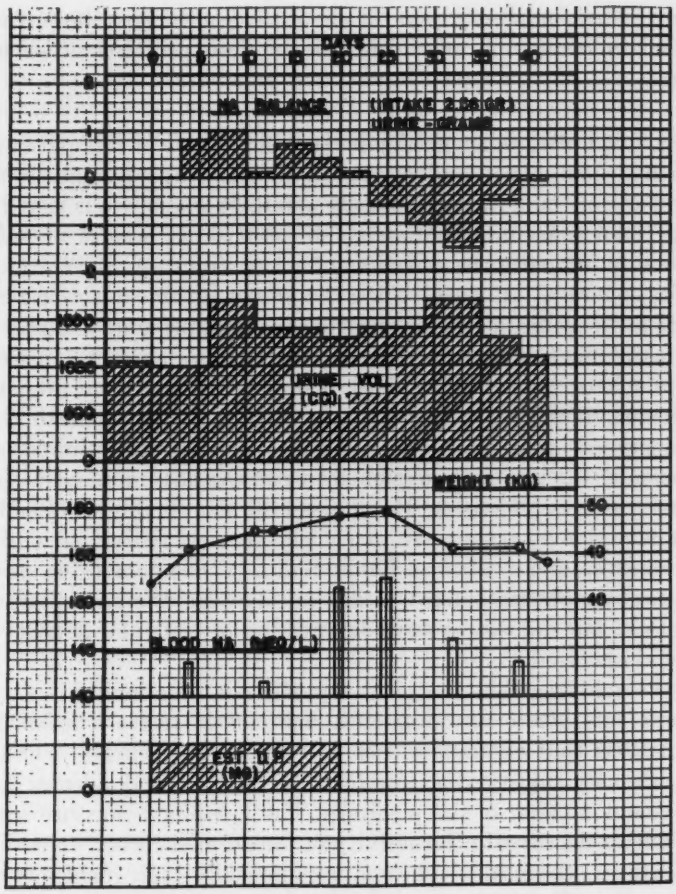

FIG. 7

During this diuresis it became normal, and eleven days after the discontinuance of the drug, was actually high (150—see Fig. 6). Glucose tolerance was not altered by desoxycorticosterone acetate (Fig. 3), and contrary to anticipation, neither was capillary permeability.

E. *The effect of estradiol dipropionate.* The patient experienced a further loss of strength and an increased tendency to fits of depression while receiving estradiol dipropionate, 1 mg. daily. Objectively, the action of the estrogen closely resembled that of desoxycorticosterone acetate (Fig. 7), although the effects were not nearly so marked, nor was the low inulin clearance of the control period altered. The secondary phase of activity associated with a lowering of blood sodium and a negative balance for that

substance lasted for twenty days, or about twice as long as the corresponding period following the administration of desoxycorticosterone acetate (Fig. 7).

DISCUSSION

The calcified intrasellar craniopharyngioma found in this patient postmortem had compressed and destroyed all but a microscopically-detectable remnant of the anterior pituitary gland. It was obvious that this remaining tissue was not functioning efficiently, but was it of sufficient magnitude to influence the activities of other structures normally coming within its sphere of influence? Upon the answer to this question rests our ability to form accurate conclusions from the data presented. Our evidence on this point must be chiefly indirect, so that any absolute answer may prove fallacious, indeed. The phasic action of testosterone preparations upon glucose tolerance, basal metabolic rate, capillary permeability, and inulin clearance might lead to the hasty conclusion that stimulation and suppression of the pituitary, dependent upon the dose employed, had produced such effects. However, Hotchkiss (13) was unable to demonstrate any phasic action upon the testis in a thirty-year-old individual with faulty spermatogenesis due to mumps. Phillip Smith (27) demonstrated spermatogenesis in hypophysectomized monkeys following the administration of testosterone, but did not observe suppression of testicular activity in the range of doses used.

Indirect evidence that the pituitary was not functioning is supported by several facts. There was complete atrophy of the testes. The basal metabolic rate was that commonly seen in Simmonds' cachexia. The glucose tolerance curve suggested a low level of thyroid and adrenal activity with a common cause in the pituitary. The low blood pressure was compatible with a decrease in the activity of the adrenal cortex. In addition to these features, the patient showed an unusually high incidence of low-grade infections involving the respiratory passages, eyes, and skin. There is reason to believe that the pituitary plays a role in our resistance to infection, probably through a specific hormone; less probably, through its influence upon protein metabolism. The secondary anemia present in this patient may indicate a disturbance in the pituitary, the thyroid, or the adrenal. We believe that the small amount of functioning pituitary tissue had little or no influence upon the action of each of the several hormones employed in this study.

The complete fibrosis of the testis, with no evidence of any normal tubular structure, suggests that this gland may have been too completely destroyed to respond to usually effective stimuli. Such a condition, however, did not interfere with the metabolic type of response to testosterone commonly to be expected at the age of 50.

The most unique single feature of this case was the severe polyuria and the diminished ability to excrete salt whenever desoxycorticosterone acetate was administered. The patient passed through a phase of temporary diabetes insipidus between the ages of 15 and 17, following which the loss of the diuretic hormone of the anterior pituitary resulted in a very low level for the exchange of water and an average daily urinary volume of approximately 1.0 liter. The prolonged administration of desoxycorticosterone produced a mild diabetes-insipidus-like picture. The high values for serum chloride and sodium may be due to the fact, stressed by Dillon (7), that desoxycorticosterone acetate raises the renal threshold for chloride.

Mulinos and his associates (20) have suggested that diabetes insipidus does not necessarily have its origin in a destructive lesion of the posterior pituitary or its connecting nervous pathways, but may be equally the result of an overactivity of certain functions of the adrenal cortex, and Corey, Britton and Silvette's (4, 5, 26) and Loeb's (18) experiments also support this view. It seems logical to believe that the capacity for such a response to adrenal cortical material would be increased in the absence of the hypophysis. This patient presented the conditions that the workers mentioned above postulated, and responded as they predicted. With the exception of the work of Anderson and Murlin (2) in a case of human diabetes insipidus, this represents the first instance, so far as we know, in which such findings have been recorded for man. At least the majority of the investigations relating desoxycorticosterone acetate to diabetes insipidus have been carried out in animals (5, 16, 20, 21, 26). However, the feeding of adrenal cortical hormones to the normal animal shows little if any effect (9, 11, 12, 28, 29) unless the dose is excessive (11, 12, 29). When prearranged conditions are used, such as excessive sodium ingestion, adrenalectomy, or hypophysectomy, the influence of posterior pituitary and adrenal preparations becomes more apparent.

In our patient, disturbances in the balances for water and salt were brought about despite a low intake of sodium chloride (approximately 2.6 gm. daily), and with doses of desoxycorticosterone acetate which would not be considered excessive in relation to such an amount of sodium for the treatment of Addison's disease (10 mg. daily). It would seem that our patient had lost at least two regulatory mechanisms for the control of salt and water balance: one in the posterior pituitary and the other in the adrenal cortex. Therefore, he was more susceptible than the normal subject to a fraction of the latter gland normally concerned with the retention of sodium. In studying the antagonistic effect of pitressin and adrenal cortical extracts in human diabetes insipidus, Anderson and Murlin (2) have demonstrated a similar interrelationship. It, therefore, seems logical to conclude that under normal conditions, adrenal cortical hormones and

posterior pituitary extracts both exert a regulatory action upon the kidney tubule, mutually antagonistic in character and concerned with the excretion of water and electrolytes.

Testosterone and methyl testosterone both exerted characteristic effects in improving muscular activity, decreasing weakness, and normalizing the glucose tolerance. The creatinuria commonly attendant upon the use of methyl testosterone was readily demonstrated.

Estradiol and desoxycorticosterone both produced a retention of sodium with an increase in the excretion of water. When all the facts are considered, it seems likely that these effects represented a decrease in the ability of the organism to excrete sodium and chloride in the absence of the antidiuretic principle of the posterior pituitary. Under such circumstances a polyuria occurred in an effort to prevent edema and to maintain a satisfactory sodium and chloride balance.

Several years ago, attention was called to the ability of testosterone preparations to cause an increase in the basal metabolic rate (3, 14, 19, 23). This action is confirmed here. In fact, the powerful metabolic influences of this hormonal material warrant a broader designation than that implied in the term, "sex hormone," now commonly in use. The improvement in muscular vigor, the variations in electrolyte metabolism, the alterations in the formation and conservation of creatine, and the changes in renal function in this and other patients receiving the drug, are among the features of its action which emphasize its fundamentally important role in maintaining the somatic integrity of the individual.

SUMMARY AND CONCLUSIONS

A 55-year-old man with an intrasellar craniopharyngioma, observed during the last five years of life, had, at postmortem, nearly complete destruction of the anterior portion of the pituitary gland and total destruction of the posterior lobe. Other endocrine organs were all markedly atrophied. In the testis this process was apparently complete.

Testosterone therapy brought about an improvement in his general condition, a decrease in glucose tolerance, a lowered excretion of creatine, and an increase to normal in the clearance of inulin. Methyl testosterone had similar effects, except for the fact that it increased rather than decreased his already pre-existing creatinuria.

Desoxycorticosterone acetate and estradiol dipropionate both caused a period of salt retention, followed by marked diuresis and a negative sodium and chloride balance. At first, high, and later, low, values for blood sodium were observed. The clearance for inulin was increased by both the hormones just mentioned, and a slight but appreciable increase in capillary permeability was simultaneously observed. All these changes were more

marked during and following the use of desoxycorticosterone acetate than they were under the influence of estradiol dipropionate.

Desiccated thyroid produced an increase in the area of the glucose tolerance curve and a rise to normal in the basal metabolic rate, while decreasing body weight, blood cholesterol, and capillary permeability.

The effects of prolactin were slight. Its use for a short period of time was associated with a gain in weight, an increase in the sodium of the blood, a slight rise in the basal metabolic rate, and a tendency towards the normalization of the glucose tolerance curve.

The commonly recognized actions of several hormones have been verified. In addition, certain features regarding water balance in relation to hormonal activity have been reported in the human being for the first time. These suggest the conclusion that the antidiuretic principle of the posterior pituitary is primarily concerned with the elimination of salt. In this respect, pitressin should be looked upon as an antagonist to certain hormonal material or materials, probably desoxycorticosterone, in the adrenal cortex.

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BILATERAL CRYPTORCHISM IN IDENTICAL TWINS[1]

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CONGENITAL anomalies in twins are relatively common, but the findings of bilateral cryptorchism in identical twins is unusual enough to prompt this report.

The monozygotic character of these twins is suggested by (1) the striking similarity in their speech and general appearance; more particularly by the similar color of the skin and eyes, the same size and shape of the hands and feet, identical skeletal proportions and whorl of scalp hair; (2) statement of the grandmother who witnessed the birth and reported that only one placenta was delivered; (3) identical response to treatment, as will be shown later. Other observations of monozygocity were not made nor deemed essential to the clinical objectives.

The twins (Leonard M. and Seymour M.) were first admitted to the clinic in July, 1942, at the age of 10, because of bilateral cryptorchism, mild stunting of growth, and underweight. They were markedly overactive and complained of anorexia and constipation.

The developmental background revealed an uneventful delivery, birth weight being 7½ pounds. They were given artificial feeding. Dentition, walking, and talking occurred without undue delay. However, growth and weight lagged at times. Childhood illnesses included measles, at 5 years of age, severe pertussis at 7, tonsillectomy and adenoidectomy at 8, and mumps at 10. They were exposed to a tuberculous mother who died soon after the twins were admitted to the clinic. Leonard showed a 2+ reaction to the Mantoux test, and a chest x-ray revealed only increased left hilar markings. Seymour showed bilateral hilar accentuation in his chest x-ray but he did not react to the Mantoux test.

The family history, except for tuberculosis, was essentially negative. The older brother was normal. The father had deserted the family, so the maternal grandmother assumed care of the children. The twins were uncooperative at home and failed to report regularly during the final period of clinical observation.

Examination revealed mild symmetrical dwarfing, a poorly developed scrotum and a small penis. There was bilateral cryptorchism and the

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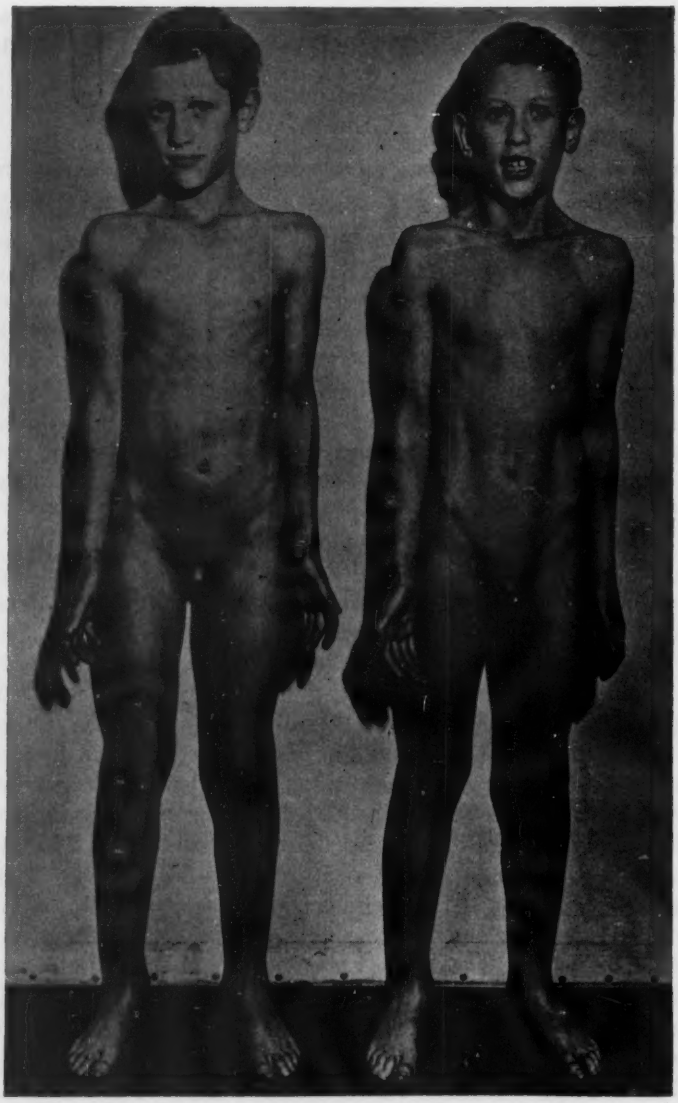

FIG. 1. Twins at 10 years of age, before treatment.

testes were impalpable in the inguinal canals. The twins' nutritional status was poor. The blood count showed a mild hypochromic anemia. X-rays revealed normal osseous development (Todd Standards). The values for serum calcium, cholesterol, and blood sugar were normal.

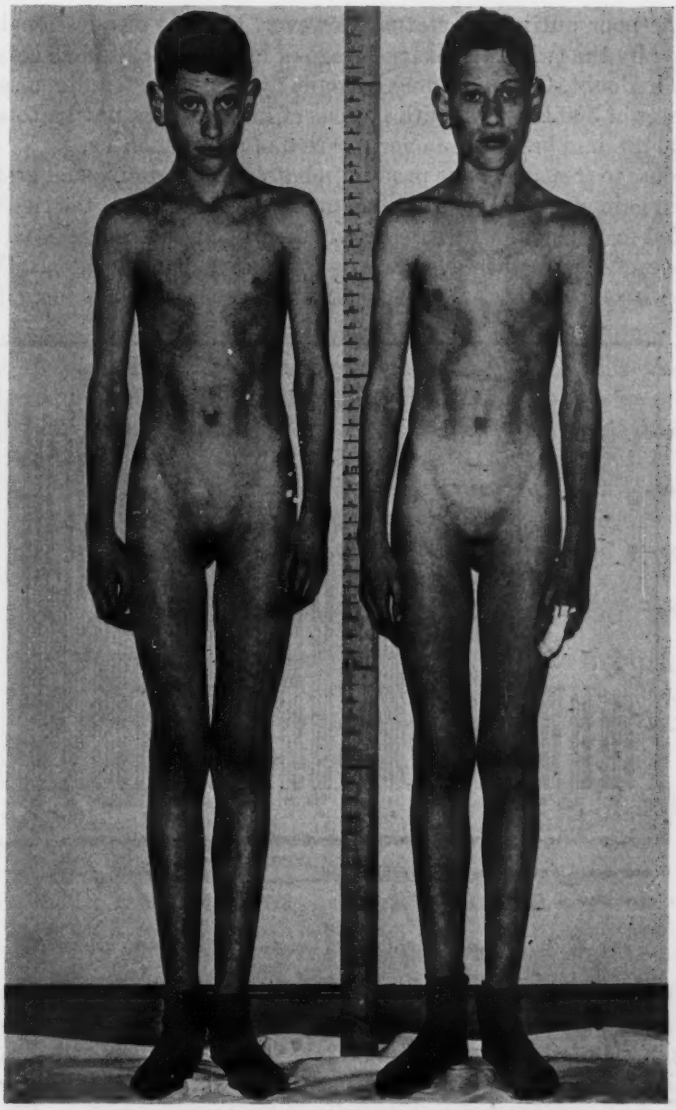

FIG. 2. Twins at 13 years of age, showing descent of testis on different sides.

Because of the obvious somatic inferiority apparent in both twins, it was deemed advisable to supplement chorionic gonadotropic therapy with methyl testosterone. Accordingly, in addition to an optimum diet, methyl testosterone was prescribed orally in doses of 50–70 mg. per week, to im-

prove the poor nutritional status. However, because of questionable cooperation by the twins, the exact dosage of methyl testosterone consumed remains in doubt. Chorionic gonadotropin* was administered in a series of eight doses of 500 I.U. each with periods of intermission, until a total dose of 19,000 I.U. had been given over a period of thirty months.

Response to treatment was prompt in both skeletal and sexual growth as well as in gain of weight. Within five months of treatment, the right testis descended in Seymour whereas the left descended in Leonard, *i.e.*, a mirror image effect (further evidence in favor of monozygocity?). The following two years of intermittent treatment was necessary to force descent

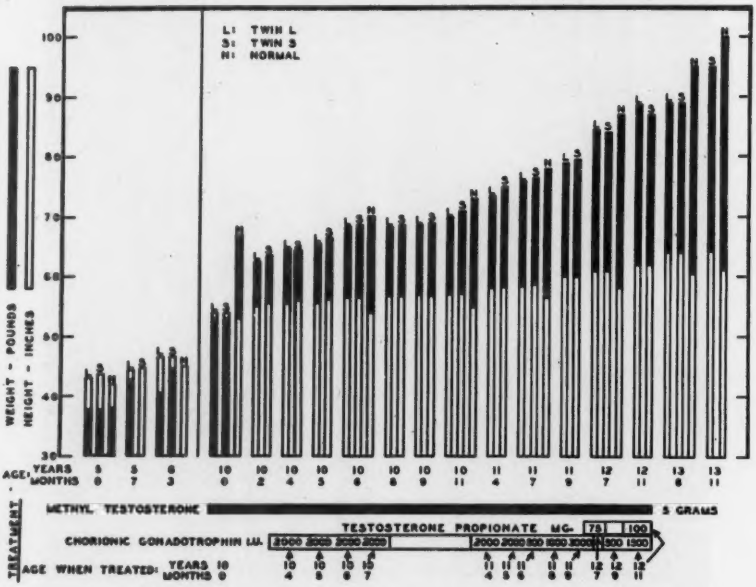

FIG. 3. Height and weight curve before and during treatment.

of the other testis. This was accomplished finally with the addition of 175 mg. of testosterone propionate given in a brief course with chorionic gonadotropin. The left testis in Seymour and the right in Leonard, descended, remaining down in a warm room or with a warm application over the scrotum, but continued to be retractile at the last observation. Precocious puberty was not induced.

The patients have not returned for further observation but the graph indicates that in so far as height and weight are concerned, both boys have attained average normal development.

* A. P. L. (Ayerst).

DISCUSSION

Dorff's (1) admirable report on controlled treatment of twins indicated the value of gonadotropins in enhancing somatic development. More critical therapeutic controls, such as withholding organotherapy from one of the twins or the administration of the chorionic gonadotropin without the testosterone to one or both twins, might have served some academic interest, but in this situation such control did not appear to be warranted nor worth-while. The beneficial effects of testosterone on nitrogen retention and skeletal growth are now well known. Moreover, when small doses of testosterone are given in conjunction with gonadotropins, the possible synergism may afford a more beneficial physiologic stimulation rather than interference with the pituitary-gonadal mechanism. This combined organotherapy seems particularly indicated in those boys who are malnourished and sexually retarded, as was the case with the twins under discussion (2, 3, 5, 6, 7, 8). Hamilton and Hubert, (4) have demonstrated the feasibility of inducing permanent testicular descent with androgens alone and in doses insufficient to stimulate erection or scrotal growth. Hence, testosterone can serve as a dynamic adjunct in the treatment of cryptorchism in selected cases.

SUMMARY

Bilateral cryptorchism in identical twins responded favorably to combined therapy with chorionic gonadotropins and testosterone. The general somatic inferiority manifested in the twins was likewise improved.

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CHRONIC CYSTIC MASTITIS AND STERILITY

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DURING the past decade it has been repeatedly demonstrated that the growth and development of the breast is largely dependent upon the ovarian hormones. In general, it has been accepted that estrogen mediates the development of the mammary ducts, and progesterone, the development of the lobular alveoli (23, 28). In animals with a persistent corpus luteum, the mammary gland shows extensive development, while in those with a short or absent luteal phase, the breast development is limited to the ducts.

The modus operandi of the sex hormones upon breast development is not as yet entirely clear. It had been thought that the action was a direct one, but the failure of estrogens and androgens to develop mammary tissue in hypophysectomized animals, and the rapid occurrence of mammary involution following hypophysectomy (28), emphasized the importance of the pituitary in the development of the breast. The discovery of a mammogenic factor (36) in the pituitaries of animals receiving ovarian hormones (11), and the separation of this factor into two parts, one secreted under the influence of estrogen and stimulating mammary duct growth, and the other secreted under the influence of progesterone and stimulating lobule proliferation (15), emphasized the reciprocal pituitary gonadal relationship. Any alteration in the balance of the various hormones in this relationship may result in abnormal changes in the tissues on which they act.

The breast, like the endometrium, reflects the hormonal stimulation from the pituitary and the ovary, and cyclically shows a proliferative phase and a secretory phase (22, 23). Excessive estrogen activity, relative or absolute, (with an associated diminution of progesterone) may result in atypical changes known as chronic cystic mastitis.

Chronic cystic mastitis has been divided into 3 types: (10, 16, 17, 18, 19) mastodynia (the painful breast), adenosis (the shotty breast), and cystic disease.

Geschickter and others have found a relative or absolute hyperestrinism to be prsent in chronic cystic mastitis. In all cases the urinary pregnanediol was low or absent (10).

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Treatment of chronic cystic mastitis has been approached in one or more of several ways.

1. The anterior pituitary has been greatly depressed or completely inhibited by enormous doses of estrogens (21) and androgens (19). Loeser (19), and later Spence (32), brought about not only a complete disappearance of the nodules in the breast with the latter hormone, but also a concomitant extreme atrophy of the endometrium.

2. The anterior pituitary has been stimulated to a greater production of luteinizing hormone and/or mammogenic factor. This has been accomplished with the administration of small doses of estrogens (10, 14, 16, 17) and androgens (1, 2, 9, 31).

3. The ovary has been stimulated to greater production of its hormones by small therapeutic doses of x-ray (27), or inhibited by large doses (35). Both these methods have been reported to result in improvement of chronic cystic mastitis.

4. The fear that chronic cystic mastitis may be precancerous has led to needless, often mutilating, surgery. Several investigators have taken this stand (5, 6, 25, 38). Others, however, believe that the incidence of cancer is too small to warrant extensive surgical procedures (12, 13, 18, 26, 33). A biopsy should be done in all cases of doubt in order to exclude malignancy. Excision of large solitary cysts may at times be advisable.

5. The fifth and probably most popular method of treatment used has been progesterone. The relative or absolute hyperestrinism may be balanced by administration of progesterone (10, 16). While this is substitution therapy, it has resulted in the alleviation of the signs and symptoms (30) of chronic cystic mastitis.

With the occurrence of pregnancy and its persisting corpus luteum and later placental progesterone, chronic cystic mastitis usually disappears or markedly regresses. Similarly, with the onset of the menopause (natural or artificial) with its decreased estrogen activity, improvement of the mammary dysplasia ensues. In the latter instance, as illustrated by several cases, the administration of estrogens to control the climacteric symptoms is sometimes accompanied by a recurrence of mastodynia or adenosis. It is interesting to note that androgens (29) and desoxycorticosterone (37) are capable of replacing the stimulative effect of estrogens upon ductal growth in the mammary gland.

In our work in sterility, the frequent occurrence of chronic cystic mastitis was particularly impressive in that group which often presented no other clinical findings (20) associated with the failure to conceive (34). The endometrial biopsy in these patients, however, was instructive. In many cases the microscopic findings revealed considerable estrogenic but

no luteal stimulation. In other instances where ovulation had occurred, there was an apparent diminution of corpus luteum activity. A typical microscopic picture is as follows: "The miscroscopic examination shows numerous endometrial glands which are moderately large and light stained. These show numerous epithelial infoldings into the lumen. The cells themselves are columnar with the nuclei near the base of the membrane. They do not show the presence of mucin to the degree usually seen in the late secretory phase. Many of the glands appear to be 'unripe' in

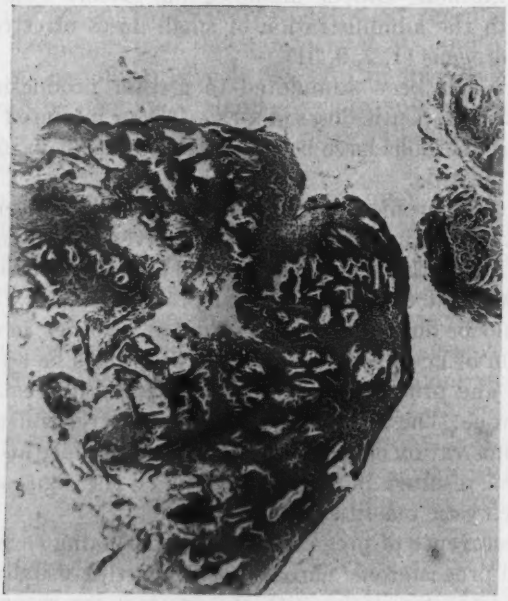

FIG. 1A. Endometrial biopsy. Low power. Obtained one day before menstruation. Glands in secretory phase.

that the full progesterone effect does not appear to be present uniformly throughout the glands."* (Fig. 1A and 1B)

It was thought that the similar findings of hyperestrinism in the breast and uterus justified the assumption that chronic cystic mastitis depends on the same hormonal imbalance that is responsible for the nonsecretory or poorly secretory endometrium in these infertile women.

In the attempt to increase the corpus luteum secretion and thus balance the estrogen-progesterone relationship, chorionic gonadotropin** was administered. This preparation was given in doses of 500–1000 I.U. two or three times weekly for the midinterval two weeks of the menstrual cycle.

Not only was there an improvement in the endometrial response in some patients formerly displaying an immature secretory endometrium, but all patients showed improvement in the chronic cystic mastitis. In several patients we were able to confirm the observations of Browne and Venning (3, 4) that the time of administration of the chorionic gonadotropin affects the menstrual cycle in different ways. When given during the near preovulatory period in large doses (1000 I.U. for three doses either daily or on alternate days) menstruation was brought forward and the cycle shortened. When given following ovulation (in the early luteal phase) in

FIG. 1B. Endometrial biopsy. High power. Lack of usual amount of mucin indicative of decreased progesterone effect.

the same dose, menstruation was postponed and the cycle lengthened. But in most patients, when given for the week preceding and the week following ovulation (as judged by basal temperatures and occasionally vaginal smears) no changes in the menstrual cycle occurred.

There is no point in discussing each individual case in detail (three typical cases are reported in the text), but some general facts concerning the present series deserve emphasis. Thirty-nine patients were treated with chorionic gonadotropin. Twenty-four of these patients came to us primarily because of their infertility. In them the mammary dysplasia was either

a secondary complaint or was ignored or unrecognized by the patient. Following treatment, 8 of these patients became pregnant. In all 24 patients the chronic cystic mastitis improved or disappeared. Fifteen additional patients complained of breast symptoms only. All of these patients showed improvement of varying degrees in the mammary dysplasia. Improvement was often noticeable during the first month of treatment and, in most cases, by the second month. In some instances, progesterone was given premenstrually to relieve persisting symptoms. Most patients were routinely given desiccated thyroid extract (one-fourth gr. to one-half gr. daily), except where contraindicated by an elevated basal metabolic rate or clinical considerations (7). A few patients with estrogenic bleeding who showed only improvement of the mammary dysplasia with chorionic gonadotropin responded with a progestational endometrium to a combination of pituitary and chorionic gonadotropin (8).

Four patients returned with recurrences after five months, eight months, two years, and three years, respectively. These patients again responded to the same treatment.

CASE REPORTS

Case 1. *Mrs. N.P.*, age 42, was seen by us in 1943 because of masses in both breasts. Her menses were regular and she had never been pregnant. On examination there were several small palpable masses towards the periphery of both breasts. The nipple area was not involved. The patient refused conservative treatment and subsequently had one mass in the right breast removed. This mass showed a chronic cystic type of change with no evidence of malignancy. Two years later, the discovery of another tumor mass in the same breast was followed by a simple mastectomy. The pathological examination revealed a fibrocystic adenoma of the breast. No malignant changes were noted. Six months following the mastectomy the patient returned to us because of enlarging masses in the left breast.

Examination in 1945 revealed a nervous individual weighing 120 pounds. Her blood pressure was 106/98. There was an absence of the corneal and gag reflexes. The thyroid was slightly enlarged. In the remaining breast were several small firm masses. The heart and lungs were negative. Vaginal examination revealed no pelvic pathology. The vaginal smear (Shorr stain) showed evidence of partial substitution therapy. The reflexes were hyperactive; there was a tremor of the fingers, and the basal metabolic rate was $+24\frac{1}{2}$ per cent.

The patient was reassured and was given mild sedation. For the chronic cystic mastitis she was treated with injections of 500 I.U. of chorionic gonadotropin three times weekly for the middle two weeks of the menstrual cycle. These were increased to 1000 I.U. the following month. After two months of therapy the masses in the left breast were definitely smaller, and after the third month they had completely disappeared.

Case 2. *Mrs. B.L.*, age 22, was seen in 1939 because of sterility of three years' duration (20). The pertinent findings in the sterility examination were a persistent proliferative type of endometrium and exquisitely tender and sensitive breasts which, she stated, enlarged to twice their size premenstrually. Examination of the breasts revealed a dense hyperplastic tender mass in both upper outer quadrants.

Administration of estrogens increased the swelling and pain of the breasts and made the masses more profuse. Treatment with small doses of chorionic gonadotropin (100–200 I.U. twice weekly) during the first two weeks of the cycle gave no improvement. When the dosage was changed to 500 I.U. three times weekly for the middle two weeks of the cycle, a rapid improvement took place in the breasts. The mass became smaller and less tender and although progesterone was required premenstrually for two months

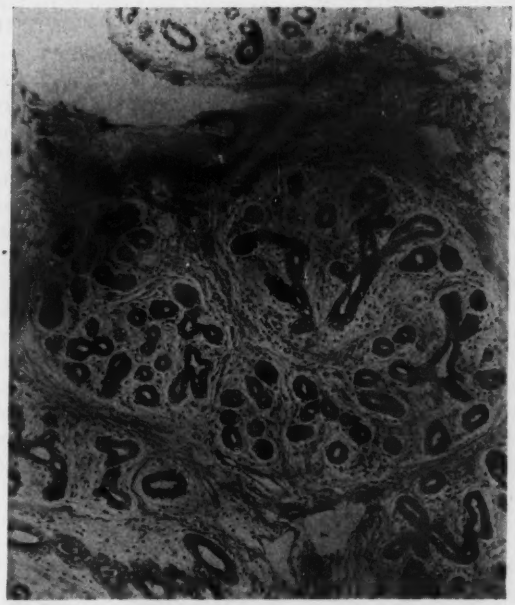

FIG. 2A. Medium high power. Section of breast showing a diffuse hyperplasia of the minute ducts without formation of acini or proliferation of any elements in the larger ducts. A lesser proliferation of the connective tissue of the breast lobules is present. In some respects the changes simulate those seen in the earlier months of pregnancy.

for the pain, the condition gradually cleared up. Four months later the patient became pregnant and subsequently delivered a normal infant. There has been no recurrence of the chronic cystic mastitis.

Case 3. *Mrs. L.W.*, age 30 years, was referred to us in June, 1945, because of her infertility. She had been seen by several physicians who had found no organic pathology to account for the failure to conceive. Her past history was negative except for the excision of a mass in her breast in September, 1942, and a similar removal of another mass in July, 1943. Several months prior to the first operation she had noticed several growing masses in both breasts. Premenstrually, these masses became larger and quite tender. The pathological findings of the first biopsy as illustrated in Fig. 2A were:

> "Microscopic examination of the breast tissue shows a diffuse hyperplasia of the minute ducts. This is evidenced chiefly by proliferation of the duct terminals, without

the formation of acini or proliferation of any elements in the larger ducts. A lesser proliferation of the connective tissue between the breast lobules is present also.

"In some respects, the breast simulates the changes seen in the earlier months of pregnancy. The picture appears to be that of the proliferation following estrogenic stimulation.

"*Pathological Diagnosis:* Proliferation of the Minute Ducts of the Breast, probably from Estrogenic Stimulation."*

The biopsy taken the following year showed similar glandular hyperplasia and slight cystic changes (Fig. 2B).

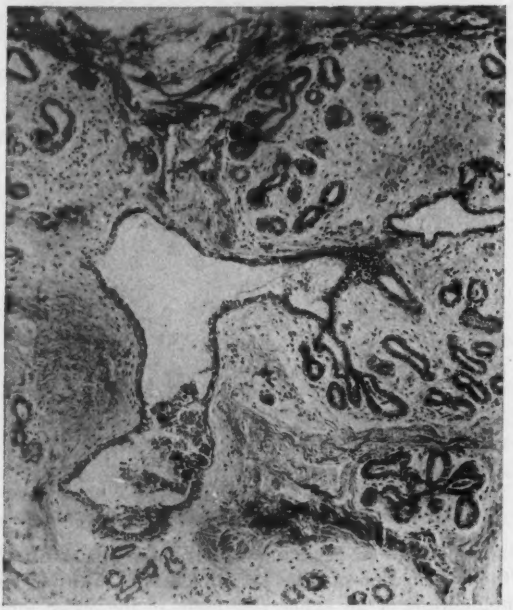

FIG. 2B. Medium high power. Section from the same breast as Fig. 2A, one year later showing slight cystic changes.

Physical examination was negative except for the breasts which were small and dense and contained several small nodules towards the periphery, especially in the upper outer quadrants. These nodules, under palpation, were of the "shotty" type characteristic of adenosis. In the right breast was a single scar.

The various tests for infertility were made. The only findings of interest were a BMR of −12.5 per cent and the endometrial biopsy which was as follows:

"Specimen consists of a few moderately thick, flat, ribbon-like uterine curettings which are soft.

"Microscopic examination reveals numerous endometrial glands which vary moderately in size and shape. They are dark staining and are composed of cells which are relatively small. The nuclei have no regular location in relation to the basement mem-

brane and the cytoplasm shows no evidence of mucin formation. These findings suggest that there has been considerable estrogenic stimulation but practically no progestational changes."

Diagnosis: Endometrium showing estrogenic but no progestational stimulation."*

The similarity of excessive estrogenic activity in both breast and uterus prompted us to try chorionic gonadotropin. One thousand I.U. were given three times weekly for the middle two weeks of the menstrual cycle. A month later there was a marked improvement in the breasts, and in two months the masses had disappeared. The injections were continued for another month. During this time the patient had been taking one-half gr. of desiccated thyroid daily. (It is interesting to note that there was also some improvement in the compatibility test.)

The patient left town and did not return to us for six months. She complained, then, of a recurrence of the masses in both breasts of one month's duration. Examination revealed the presence of a firm cystic mass about the size of a grape one inch above the nipple of the right breast. There was a hyperplastic mass of breast tissue in the upper outer quadrants of both breasts but more marked in the right. Chorionic gonadotropin was given in 1000 I.U. doses daily for five days (from the eighteenth to the twenty-second day of the cycle). The fullness and tenderness of the breasts were eased by two injections of 10 mg. each of progesterone. The menstrual period was delayed one week. This is significant in view of the fact that her periods had been regular up to this time.

Reexamination of the breasts just prior to menstruation revealed an unquestionable reduction in the size and density of the mass in the right breast and an even more appreciable reduction of the hyperplastic breast tissue on the right side. The hyperplasia of the left breast had disappeared completely.

SUMMARY

Chronic cystic mastitis is the result of a relative or absolute excess of estrogens producing abnormal proliferation of the mammary ducts. Although the estrogenic level may be within normal limits, pregnanediol has been shown to be low or absent. This hormonal imbalance results in one of the varieties of chronic cystic mastitis.

Review of the literature reveals ample evidence indicating the endocrine origin of chronic cystic mastitis, but no suggestion of a possible relationship between this condition and infertility could be found.

In a series of 24 functionally infertile women with mammary dysplasia, there was a striking parallelism between the occurrence of chronic cystic mastitis and an absent or poorly developed secretory endometrium. This indicates that the endometrial and mammary abnormalities are both manifestations of disturbed estrogen-progesterone balance.

Both this group, and a second group of 15 patients complaining of mammary symptoms alone, responded to treatment with chorionic gonadotropin with improvement or disappearance of the chronic cystic mastitis. Eight of the 24 infertile women subsequently became pregnant.

ACKNOWLEDGMENTS

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THE USE OF METHYL TESTOSTERONE IN THE TREATMENT OF PREMATURE INFANTS

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"SPECIAL studies have shown that at least 5 per cent of all infants born alive are born prematurely. This means that more than 114,000 infants were born prematurely in the United States in 1938. In the same year, more than 31,000 neonatal deaths were reported by the United States Census as directly due to premature birth. The national neonatal mortality rate from this cause in 1938 was 13.9 per thousand live births" (6). In the State of California, there were 47.0 prematurities per 1000 live births in 1943 and 52.1 per 1000 in 1944. These figures indicate the importance of the problem, since the incidence of prematurity for California, at least, has apparently increased above that predicted for the birth rate.

Because of the difficulty in estimating prematurity from any single criterion, particularly from the period of gestation, the American Academy of Pediatrics advocated several years ago, that a standard measure of weight be used, and that all infants weighing 2500 gm. (approximately five-and-one-half pounds) or less, be determined premature. The California Department of Public Health is now requesting hospitals to include in their annual report of maternity patients, information on the number of infants born alive weighing 2500 gm. or less. By the use of such a criterion more accurate statistical data may be compiled.

The application of physiologic principles to the treatment of prematurity is not new. Several observers, Einhorn (1), Martin (3), Potter (5), and others, have employed estrogens with varying degrees of success. Moncrieff (4) used thyroid as a general metabolic stimulant, and Giuffrida (2) injected chorionic gonadotropin soon after birth without noticing any beneficial effects.

In reviewing this work, it appeared to us that, with one exception (the thyroid experiment), these procedures were based solely upon the fact that the mother's tissues were bathed in estrogens, gonadotropins, etc., without there being a more comprehensive understanding of the part these substances play in the infant metabolism. Since nitrogen storage and utilization are the physiologic effects desired, it occurred to us that perhaps testosterone, one of the most important metabolizers of nitrogen now known, might be a rational drug for clinical trial.

This report concerns 15 premature infants. The birth weight in all but one was less than four pounds (1920 gm.). The period of gestation in all

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of them was approximately seven months. They were given 2.5 mg. of methyl testosterone every twelve hours for from three to seven weeks. There were also some 15 others whose birth weights ranged between 2000 and 2500 gm., who are not considered in this paper, as it is reasonable to assume that most, if not all, of these infants would have survived while on routine care.

The basic or routine care of this entire group of premature infants was essentially the same as that previously employed except for the use of

TABLE 1

Name	Birth Weight		Discharge Weight		Discharge Age
	Lbs.	*Gm.*	*Lbs.*	*Gm.*	
(1) Boy A	3–10	1740	6–4	3000	6 weeks
(2) Boy Am	3–6	1620	6–2	2940	7 weeks
(3) Boy M—#1	3–9	1710	6–1	2910	4 weeks
(4) Boy M—#2	3–12	1800	6–8	3120	4 weeks
(5) Girl B	3–9	1710	6–1	2910	5 weeks
Twin died in 12 hrs.					
(6) Boy D	3–8	1680	5–12	2760	4 weeks
(7) Girl M	2–12	1320	6–4	3000	7 weeks
(8) Boy L. G.	3–12	1800	5–14	2820	4 weeks
(9) Girl L	3–6¼	1628	5–10	2700	2 weeks
(10) Boy R	2–12	1320	4–12	2280	6 weeks
(11) Girl L	3–3	1530	5–14	2820	5 weeks
(12) Girl	3–8	1680	5–4	2520	4 weeks
(13) Boy L	3–13	1830	6–2	2940	4 weeks
(14) Boy H	3–12	1800	5–8	2640	5 weeks
(15) Boy G	4–1	1950	5–8½	2655	3 weeks

testosterone, and consisted of the following: The infant was placed in an incubator immediately after delivery. Nothing was given by mouth for twenty-four hours, at which time feedings every four hours by gavage were started. A mixture of five per cent CO_2+95 per cent Oxygen was given for five minutes before and after gavage for the first few days or longer, as was considered necessary. This latter procedure has been used by one of us to ameliorate the attacks of syncope so commonly present in prematures at feeding time. Formulae consisted of either Olac or Similac to tolerance. Hypodermoclyses of 5 per cent glucose in Ringer's solution in quantities of 30 to 50 cc. twice a day and later once a day, were given until the weight gain was established. Stimulants such as caffeine, epinephrine, alpha-lobeline,

and coramine were used in appropriate doses as necessary. In general, infants were gavaged until they weighed five pounds and in the past this plan has given satisfactory results. However, there are some infants who seem devoid of that functional spark necessary to initiate a vigorous body metabolism. It was this type of infant we hoped to help.

Since a weight of 2500 gm. is considered the maximum consistent with a diagnosis of prematurity, we chose only those infants weighing below 2000 gm., with a low average of 1676 gm., in order to give the procedure the most critical trial. We are aware that the limited number of patients presented here is far too small to warrant definite conclusions; nevertheless, the striking performance of these infants seems to justify a preliminary report.

The first infant studied required almost continuous oxygen and repeated stimulation but continued to lose weight in spite of what was considered adequate routine treatment and care. Methyl testosterone in a dose of 2.5 mg. was added to the gavage every twelve hours, and in thirty-six hours it was possible to discontinue the oxygen and stimulants. He promptly began to gain weight and continued to gain steadily.

One infant did not receive methyl testosterone for about five days, because the supply ran out and his reversion to a lesser state of well-being and failure to gain were most striking. It appears that from twenty-four to forty-eight hours of medication are necessary before signs of its beneficial effects are noticeable. We have noted no untoward effects.

The heavier infants not considered here did better, in general, than has been our past experience with them. It might also be stated that four small infants weighing from five and a half to six pounds (2640 to 2880 gm.) who failed to regain their birth weights by 8 to 10 ounces after three to four weeks, despite good appetites or gavage with adequate or better-than-adequate caloric intakes, hypodermoclyses and no illnesses, promptly began to gain weight after the administration of 2.5 mg. of methyl testosterone every twelve hours was started.

Improvement in the general reactions and in the appearance of well-being of the treated infants was sometimes remarkable. It has been commented about repeatedly by nurses who have had years of experience in the care of premature infants in the same institution. We bring out this point because of the healthy skepticism of these same nurses when the work was initiated. When questioned, they said that the infants, after thirty-six to forty-eight hours of treatment, acted more like normal, full-term infants than premature ones.

Of the fifteen infants reported, we believe that seven would probably have died had it not been for the use of testosterone. The other eight most likely would have survived without other than routine care. How-

ever, their progress appeared to be greatly enhanced by testosterone. Because the fate of the premature infant is unpredictable, at best, and because of the obvious difficulties in getting laboratory work in the newborn, this report must, of necessity, be made from clinical impressions rather than from factual data, except for gain in weight.

It may be that we have been fortunate in having fifteen good, premature infants who would have lived in any event. However, since adding methyl testosterone to the treatment, we have not lost a premature infant who lived over thirty-six hours. It is not weight gain alone which has been so satisfactory but the rather dramatic effect the medication has had on body vigor. The infants have had few, if any, cyanotic attacks, practically no digestive disturbances such as vomiting and abdominal distension, and food is well digested with normal-appearing stools.

Under ordinary circumstances, the addition of methyl testosterone to the feeding is a simple and satisfactory method of administration and is apparently well tolerated. Under certain circumstances, especially when the infant was in very poor general condition, testosterone propionate in a dose of 2 mg. intragluteally, was employed immediately after delivery, and repeated in twelve hours. These few infants did not survive. It appears to us that an infant must have a sufficient backlog of inherent vitality to maintain itself for twenty-four hours. After this, testosterone may be the determining factor in survival for an unknown percentage of infants who are too physiologically inert to initiate a vigorous metabolic function spontaneously.

We had no precedent for dosage but decided to give about one-fourth of the minimal amount necessary to establish a satisfactory effect on nitrogen storage in the average preadolescent child, namely, 2.5 mg. every twelve hours. It is possible that owing to some peculiar effect on nitrogen metabolism, testosterone propionate intramuscularly would be preferable to methyl testosterone. Methyl testosterone lends itself to ease of administration, however, without the necessity of the trauma incident to repeated hypodermics. It is also possible that our dose is too large or too small for the maximum physiologic effect.

Studies are in progress in a large hospital wherein we hope to administer testosterone to every other premature infant weighing less than 2000 gm. over a period of a year or longer. The results should either verify or refute our present optimistic impressions.

SUMMARY

A preliminary report is presented wherein fifteen premature infants of both sexes, weighing less than 2000 gm. (average 1676 gm.), with an approximate 50 per cent prediction of mortality, were given 2.5 mg. methyl

testosterone in their feedings every twelve hours over a period of from four to seven weeks. All fifteen infants survived. The initial weight loss was minimal and weight gain and vigor were initiated early. There were no untoward effects.

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GASTRIC DYSFUNCTION OF HYPOESTROGENIC ORIGIN—TREATMENT WITH BENZESTROL

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THE majority of clinical reports, which have been voluminous in recent years, have dealt more or less with the neurologic and cardiovascular manifestation of estrogenic deficiency, while the gastro-intestinal disturbances often complained of by these patients have received little or no attention. It is upon these possible gastro-intestinal manifestations of estrogen deficiency, and the response of such symptoms to treatment with estrogen, that attention is focused in this report.

Gill (4) considers the symptom complex of nausea, vomiting and pain, associated with disturbances of the other systems in women having hypo-ovarianism, as psychogenic in origin. Engle (2), likewise, states that some degree of psychoneurosis is present and may have been present some time before manifestations of hypo-ovarianism. Regarding the question of a relationship existing between the ovary and gastric secretion, Sandweiss, Saltzstein, and Farbman (9) have pointed to a possible ovarian hormone action, which, acting through the anterior pituitary, might possibly exercise a regulatory function on gastric secretion and function.

Similar suggestions have been made with regard to the endocrine-gastric relationship in the male. DeMuro and Marconi (1) made a study of the gastric secretory response in males following the use of orchic extract and testosterone propionate. They reported a definite response in those patients presenting symptoms of achlorhydria and hypochlorhydria after treatment with the male sex hormone. There was an increase in both the amount and the acidity of the gastric secretion with improvement of the gastric function and in general well being. They attributed the improvement of gastric function partly to a hormone-stimulating effect upon the gastric mucosa and partly to a restoration of balance of the autonomic and sympathetic nervous systems.

In the course of investigating benzestrol,[1] a relatively simple, inexpensive estrogen (3, 6, 7), it was noted by the author (5) that a few of the women who had been under treatment with this estrogen because of so-called classical menopausal symptoms had been quite markedly or com-

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[1] During the early portion of the work, benzestrol was obtained through the courtesy of Dr. E. W. Blanchard, Research Laboratory, Schieffelin & Co., New York City.

pletely relieved of some vague chronic gastric distress or nausea. No specific cause for this gastro-intestinal distress had been found and it had not been relieved in some by previous treatment with natural estrogens and had been definitely aggravated by stilbestrol in others. Further investigation of women in the menopause disclosed the fact that 15 or 20 per cent had some definite distressing gastric symptomology associated with the usual climacteric symptoms. Quite often definite organic disease of the gastro-intestinal tract, kidneys, liver and gall bladder, pancreas and pelvic organs, was responsible for this gastric distress. However, there were a considerable number of cases without any tangible evidence of disease to account for the gastro-intestinal symptoms, in spite of a careful history, physical, laboratory, and x-ray examination, and when indicated, gastroscopy. Frequently, their symptoms had been attributed to a functional nervous disturbance, but response to treatment by use of sedatives, antispasmodics, and assurance was usually unsatisfactory or temporary.

Because of the rather unique relief of some of the gastro-intestinal distress so frequently complained of in the menopausal group of women, further investigation was made of younger premenopausal women and also of women past the menopause. In all, 64 women, from 24 to 56 years of age, who had functional gastric distress and in whom there was laboratory or clinical evidence of hypoestrinism, were studied. Follow-up studies sufficient to obtain complete records were made in 43 cases. Evidence of estrogen deficiency was obtained by clinical history, physical examination, vaginal smears, and endometrial aspiration biopsy made and stained according to the technic of Papanicolaou and Shorr (8). The vaginal smears and endometrial biopsies were also used to follow the response to therapy. In addition to the data as described above, all patients had the following routine examinations: two or more urinalyses, complete blood counts, sedimentation rate, serological test for syphilis and brucellosis, and when indicated, blood chemistry studies, gastric and stool analyses, and x-rays of the gastro-intestinal tract, gall bladder, and kidneys. Gastroscopy was also performed if there was any question about pathology in the stomach. Test diets and elimination diets were used if indicated.

In final analysis, relief following benzestrol therapy had to be quite definite and very prompt in order to classify these gastric symptoms as the result of hypoestrinism. In most of these patients other symptoms were frequently associated with the gastric symptoms and relief was usually about parallel.

Dose. The usual initial dose of benzestrol was 5 mg. given intramuscularly, from one to three times a week, until symptoms were relieved; then the dose was reduced to once every seven to ten days as improvement progressed. After one to three months, with symptoms definitely con-

trolled, one injection per month of 3 to 5 mg. was usually sufficient to maintain relief. In those premenopausal women in whom the periods were still regular, benzestrol was administered one week after cessation of the menses. The parenteral administration may be supplemented by the oral administration of benzestrol, 2 mg. three times a week at bedtime. After four to five months, small doses orally one to two times a week may suffice. However, in women with severe reactions at the menopause, at times

TABLE 1. SUMMARY OF RESULTS OF BENZESTROL THERAPY UPON GASTRO-INTESTINAL SYMPTOMS IN PATIENTS EXHIBITING SYMPTOMS OF HYPO-OVARIANISM

Type of patient	Number in group	Age	Symptoms (All not present in all cases)	Results (Improvement in gastro-intestinal symptoms)
Pre-menopausal	20	24–48 (35 Av.)	Epigastric distress, soreness, gas, nausea, occasional vomiting. Menses essentially regular although often scant. Vasomotor and other menopausal symptoms absent.	Complete relief....16 Marked improvement with only occasional episodes of G.I. distress..... 4
Menopausal	23	25–54 (43 Av.)	Gastro-intestinal symptoms same as above. Vasomotor and other usual menopausal symptoms present. Menses irregular or absent.	Complete relief....14 Marked improvement with only occasional episodes of G.I. distress..... 9

for short periods or for periods of a year or so, the only method of control may be the parenteral administration of 5 mg. doses.

The result of administration of benzestrol to a series of 43 carefully controlled patients, exhibiting evidences of hypoestrinism and gastro-intestinal disturbances with or without the more common vasomotor symptoms of the menopause or symptoms of menstrual upset, have been summarized in Table 1. The previous medical history, marital status, number of pregnancies, and weight of these patients, were recorded. Since there was no correlation between these data and the symptomology or response to treatment, they are omitted from the table.

A brief protocol on four of the women follows:

No. 1. *J.E.T.*: premenopausal; age, 29 years; weight, 115 pounds; single; no pregnancies; previous medical history: appendectomy and hemorrhoidectomy; no sequelae. Symptoms: asthenic, poor digestion, gastric distress, stomach feels "jittery," pain, nausea

after meals, no relief with diets or sedatives. X-ray of the gastro-intestinal tract, negative; gastric analysis, normal; BMR, −10 per cent; vaginal smear and suction biopsy showed slight estrogenic deficiency. Benzestrol given by intramuscular injection, 3 to 5 mg. once a week for two months; then once a month during the first postmenstrual week for four months; maintained for last year on benzestrol orally, 5 mg. once or twice a week. Gastric distress gradually improved and disappeared in two months, and has not recurred.

No. 2. *M.D.:* premenopausal; age, 43 years: weight, 138 pounds; divorced; no pregnancies; no previous medical history. Symptoms: epigastric distress, pressure, flatulence, nausea after meals; menses regular. X-ray examination of gastro-intestinal tract and gall bladder, negative. Slight to moderate estrogenic deficiency. Benzestrol given intramuscularly, 3 to 5 mg. once a week for two months, then twice a month for three months; oral benzestrol 2.5 mg. twice a week for six months. Complete relief of gastric distress in two to three weeks. No recurrence.

No. 3. *K.J.:* menopausal; age, 45 years; weight, 132 pounds; single; no pregnancies; no medical history. Symptoms: considerable amount of gastric distress, bloating, sometimes nausea after meals, poor appetite, constipation; menses scant for one year and ceased in 1944; hot flashes and palpitation. X-ray of stomach and gall bladder, negative, gastric analysis, normal. Moderate estrogenic deficiency. Benzestrol given intramuscularly, 5 mg. once a week for one month, then once a month for six months. Gastric distress, nausea, and hot flashes gradually disappeared in three weeks. Improved bowel function. Has remained symptom-free.

No. 4. *A.J.R.:* early menopause; age, 46 years; weight, 118 pounds; married; four pregnancies; treated for duodenal ulcer 1940, no recurrence. Symptoms: midepigastric pain, nausea, and vomiting; no relief with dietary, sedative, or antacid therapy; menses scant but regular, nervousness and hot flashes. X-ray of gastro-intestinal tract, colon, and gall bladder, negative; electrocardiogram, negative; gastroscopy, negative. Moderate estrogen deficiency, Benzestrol given intramuscularly, 5 mg. twice a week for three months, continuing on benzestrol orally, 5 mg. tablets two to three times a week. Gastric symptoms reduced 80 per cent in three weeks, with complete relief in three months; has remained symptom-free for nine months.

As can be seen from the table and the above sample protocols, the synthetic estrogen, benzestrol, was found to be effective in eradicating the gastro-intestinal as well as the more usual subjective symptoms associated with estrogen deficiency. Some of these women have been under observation for two to three years, and in some in whom a relapse of symptoms occurred months or even a year later, a satisfactory therapeutic response was again obtained by the same course of therapy.

Maintenance of an estrogen balance was obtained without difficulty and it would appear that the cumulation and elimination of the drug must be at a rate compatible with physiological needs and tolerance. No untoward side-reactions were observed following benzestrol therapy, as had been observed by the writer following the use of other synthetic estrogens.

As might be expected, the menopausal patients, having a greater variety of symptoms, were especially benefited and their improvement in "well-

being" was proportional to the degree of hypo-ovarianism existing prior to therapy. It was possible for them to perform more mental and physical work because of increased vigor, greater emotional stability, and improved concentration. While the therapeutic effectiveness of the drug was noted by the subjective relief of symptoms, the vaginal smear method of Papanicolaou and Shorr was used as an objective index of improved estrogen balance, and where indicated, endometrial biopsies were made by the suction curettage method. The vaginal pH was determined by nitrazene paper.

The important point to be brought out is that a large proportion of these patients were seen because of the primary presenting symptoms of gastro-intestinal distress. In most of the premenopausal group, and in many of the menopausal patients, the usual subjective symptoms of estrogen deficiency were absent altogether or so slight that they had not concerned the patient. Many of these patients had had various courses of treatment directed primarily at their gastro-intestinal symptoms, without relief. Only upon objective examination, vaginal smears or endometrial biopsy, was the estrogen deficiency recognized. This leads to the suggestion that an estrogen deficiency be suspected in women presenting symptoms of gastro-intestinal distress, without findings of gastro-intestinal pathology, and in many instances, presenting few, if any, symptoms of hypo-ovarianism. If facilities are not available for the performance of objective tests for this hormone deficiency, a course of adequate estrogen therapy may serve as a diagnostic test. Such therapy, when given with proper regard for the estrogen-pituitary balance in the patients still menstruating, can do no harm and may lead to relief. In the author's opinion, the use of injectable preparations results in the most prompt control of symptoms of estrogen deficiency. After control has been established, the improvement may be maintained with less frequent, smaller amounts by injection, or by oral administration.

SUMMARY

1. Sixty-four women of various ages whose primary presenting symptoms were those of gastro-intestinal distress were found to have varying degrees of estrogen deficiency.

2. Treatment of these patients with the synthetic estrogen, benzestrol, in oil by intramuscular injection, or orally in tablets, resulted in almost complete relief of gastro-intestinal symptoms. Complete records were available on 43 of these patients, 30 of whom had complete relief and 13 marked improvement.

3. The relief of the gastro-intestinal distress was accompanied by objective improvement in estrogen balance.

4. It is suggested that an estrogen deficiency may be the underlying etiology in gastro-intestinal distress in patients in whom the usually recognized symptoms of hypo-ovarianism are slight or even absent.

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Letter to the Editor

TO THE EDITOR:

ANDROGENIC ARREST OF FAMILIAL ENURESIS IN 75 CHILDREN

UNINTENTIONAL and unconscious diurnal or nocturnal discharge of urine may be a Mendelian recessive trait. It occurs in the absence of local or systemic disease in one or more children of the same family with a predecessor's history of enuresis in childhood. While the symptom tends to clear up at maturity, the adult remains subject to urinary frequency, urgency, and nocturia despite unwillingness to admit it. This lack of bladder control is a behavior pattern usually inherited from the affected parent or grandparent whose lower half of the body the child favors, irrespective of sex or social status. The familial defect is observed in about one-third of patients with urinary incontinence after the third year of life. They rarely fail to wet the bed night after night, year after year, without being awakened by the incident. Some have such an urgent and frequent desire to empty the bladder during the day that their clothing becomes wet during periods of nervous tension and cold weather, by day, and regularly during the night, in spite of intelligence or training. The others remain constantly wet with offensive decomposing urine, day and night, no matter what therapy is instituted.

Urination is a reflex act involving the musculature of the bladder, spinal centers, efferent and afferent nerves. Any local or systemic disturbance interfering with this regulatory mechanism will inhibit the process even during sleep. Various attempts have been made to determine the nature of these disturbances inside and outside this reflex arc without considering the degree of maturity of the urogenital structures for the age of the child.

Nature provided an elaborate mechanism for regulating so simple a function as emptying the bladder. In a sense, it works like a combination safe whose purpose is not so much the opening of the bladder or safe at the proper time but of preventing its being emptied at some other time. The combination of nerve impulses involved in bladder control, in the normal child, responds to training and will, in the presence of adequate maturations of the urogenital mechanism.

In enuresis the infantile condition persists with the detrusor muscle holding mastery over the sphincter. Disparity between the innervation of

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the two sets of muscles allows the detrusor, normally held in check by the sphincter, to overcome the comparatively weak action of the latter. But enuresis often clears spontaneously at puberty when sexual maturation strengthens the action of the sphincteric mechanism. Trousseau (5) attributed functional enuresis to an irritable bladder. Cain (1)demonstrated an immaturity of the musculature. Hoffman (3) attempted to improve its development by anterior-pituitary-like hormones. Schultz (4) succeeded with male sex hormone in a random group of enuretics. We have found this immaturity to be especially applicable to children with familial enuresis. While the condition clears by adolescence, the affected child is still subject to urinary frequency, urgency, and nocturia.

A child over three years of age who has not learned to control his bladder is evaluated for local irritation from foci in the genito-urinary tract or adjacent structures, *i.e.*, urologic malformation, cystitis, calculus, vaginitis,

TABLE 1. DISTRIBUTION OF FAMILIAL ENURETICS TREATED WITH ANDROGENS

Age	Sex		Effect of Treatment		
Years	Boys	Girls	Failed	Improved	Cured
4–8	24	8	3	6	23
8–12	14	5	2	2	15
12–16	18	6	1	2	21

balanitis, intestinal parasites, anal polyp or fissure; or for systemic organic dysfunction, *i.e.*, spina bifida occulta, epilepsy, brain or cord lesion, diabetes mellitus or insipidus, allergic disease, intercurrent infection, neuropathic personality, or mental retardation. The vast majority of cases are functional in origin and devoid of organic disease of the urogenital or nervous systems. They suffer from familial tendency, emotional conflict, or improper training.

Seventy-five normal children of familial enuretics with and without emotional and training difficulties, have been studied since 1940 because they failed in all forms of therapy. Boys predominated in this group (3:1) probably because of their greater difficulty in learning bladder control. They actually go through two successive trainings, first sitting down, then standing up. Treatment consisted of 10 to 30 mg. of methyl testosterone daily in divided doses for one to three months. If oral administration produced no significant improvement within a fortnight, it was supplemented by the intramuscular administration of testosterone propionate in a dose of 10 mg. weekly. Fluid intake was restricted throughout the day except

for milk, morning and noon, cracked ice between meals, and rinsing of the mouth with water to quench thirst.

Mothers were advised to remain unemotional about wetting episodes because parental anxiety has an untoward influence on the child's psyche. If the maternal bond had been sufficient, the child's resolve to please his mother would have permeated the deeper layers of his mind and led to better control of the nervous mechanism of the bladder. With insufficient desire to please his mother, the child is concerned with his own comfort and empties the bladder when tension causes the slightest discomfort. The situation was explained to both mother and child to establish better decorum between them.

Most children were anxious to co-operate after years of wetting, shame, and embarrassment. The androgenic material gave them more confidence and less anxiety about bladder control. Indeed, some of the associated emotional disturbances eased with improvement. Nocturnal enuresis diminished in both frequency and urgency in from three to ten weeks, but diurnal enuresis was more resistant, requiring months to clear, in four cases. Until such improvement became manifest, the child was awakened once or twice during the night to void. As the condition cleared, testosterone was gradually diminished and fluid intake slowly resumed without return of the symptom for six months to one year, in the cases reported. Each child was informed of the nature of his infantile difficulty, the method of attaining his bladder control, and the need for assuming complete responsibility for his body behavior in an effort to make him master of a mature function.

SUMMARY

Fifty-nine normal children with familial enuresis were cured by oral administration of methyl testosterone or intramuscular injection of testosterone propionate for a period of three to ten weeks. Ten children were improved in fifteen weeks, but six failed to benefit from this form of therapy.

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Book Review

SELYE, HANS. *Encyclopedia of Endocrinology, Section IV, The Ovary, Vol. VII, and Vol. VII (Ref.).* Montreal, Richardson, Bond and Wright, 1946.

These two volumes, one of text with an extensive index, the other of references, are the second section of a great, living Encyclopedia of Endocrinology which is being compiled by Dr. Selye. He has long advocated that medical science would benefit from systematic reviews of various phases of various special subjects, and has undertaken this work to illustrate his idea, as an experiment in one field, Endocrinology. The success of this work's first section, the "Classified index of the steroid hormones and related compounds," led him to continue with the present section.

Selye has written a highly interesting Foreword in which he effectively portrays his vision of the great encyclopedias he projects for each field of medicine. Unlike many other dreamers, he has offered a tremendous work as an example. The Foreword reveals some of the interesting developments along these lines that we may anticipate when the world's social organization is further perfected to support scientific effort.

The first of the volumes, containing the text, is printed in a loose-leaf system in order to minimize the expense of keeping the material up to date with supplements. It is stated that the new material will be issued in such a way that sections with new pages can be slipped into the places of the old. An elaborate system for numbering of pages is invented for this purpose. The illustrations are beautifully clear and are very numerous. The many references in this volume of text are cited in a system aimed to make the reading easy, yet to have the references easily sought.

The reference volume is not loose-leaf and is reproduced by a photographic ("Photorepro") process directly from the manuscript typed by electromatic typewriters. The author states that this was done in order to reduce the possibility of errors in transcribing. The result is a very legible and undoubtedly highly accurate product.

The references are listed in alphabetic order, and each has an identification number. The only sacrifice detected by the reviewer is the omission of the final page of each reference. No doubt this would have been too much to expect in such a work, but nevertheless would have added a certain benefit.

This encyclopedia deserves to be included in every major reference library and in every laboratory of endocrinology.

KENNETH WADE THOMPSON, M.D.

Announcements

Nominations for Awards of the Association

Three awards for meritorious work in endocrinology will be given at the next annual meeting of the Association. These include the Squibb and Ciba Awards which have been given in the past, and a new award, which will be known as the Ayerst, McKenna & Harrison Fellowship in Endocrinology, to be given for the first time in 1947. A special committee of five members of the Association chooses the recipients of these awards, subject to ratification by the council, and each member of the Association has the privilege of making one nomination for each award.

Nominations for the awards should be made on special application forms which may be obtained from the secretary. A nomination should be accompanied by a statement of the importance of the nominee's contributions to endocrinology and by a bibliography of his most important papers, with reprints if possible. Application forms may be obtained from the secretary and all nominations should be sent to Dr. Henry H. Turner, Secretary, 1200 North Walker Street, Oklahoma City 3, Oklahoma, not later than March 15, 1947.

THE E. R. SQUIBB AND SONS AWARD

The E. R. Squibb and Sons Award of $1,000.00 was established in 1939. It was given in 1940, to Dr. George W. Corner; in 1941, to Dr. Philip E. Smith; in 1942, to Dr. Fred C. Koch; in 1944, to Dr. Edward A. Doisy; in 1945, to Dr. E. C. Kendall; and in 1946, to Dr. Carl G. Hartman. No award was made in 1943. No age or other special limitation is stipulated by the donor of the award. Thus far, it has been given for long-continued work of a high quality.

THE CIBA AWARD

The Ciba Award was established in 1942 and is given to an investigator not over 35 years of age. No recipient was selected in 1943. In 1944, the award was given to Dr. E. B. Astwood; in 1945, to Dr. Jane Anne Russell; and in 1946, to Dr. Martin M. Hoffman. The award is for $1,200.00. If the recipient chooses to use the award to aid in working in a laboratory other than the one in which he normally is located, the award will be increased to $1,800.00.

THE AYERST, McKENNA & HARRISON FELLOWSHIP

This award was authorized by the Council at the 1946 meeting in San Francisco and will be presented for the first time at the 1947 annual meet-

ing in Atlantic City. The annual stipend is $2,500.00 and may be renewed at the discretion of the Committee on Awards. Applicants for this fellowship shall fulfill the following requirements:

1. They must possess the degree of Doctor of Philosophy or Doctor of Medicine or their equivalent. It is suggested that no restriction be placed on age, but that preference be given to applicants who have recently completed requirements for their Ph.D. or M.D. degree.
2. They must present evidence of scientific ability as attested by studies completed or in progress and/or the recommendation of responsible individuals.
3. They must submit a program of proposed study.
4. They must indicate one or more institutions where the proposed program shall be carried out.
5. They must submit statements of approval from the investigators with whom they propose to conduct their research.
6. They must serve full time if awarded a fellowship. A small amount of time (10 to 15 per cent) may be allotted for course work or for participation in teaching, the latter purely on a voluntary basis.

Annual Meeting of Association

The 29th annual meeting of the Association for the Study of Internal Secretions will be held Friday and Saturday, June 6th and 7th, 1947, in the Viking Room of Haddon Hall Hotel, Atlantic City, New Jersey, preceding the Centennial meeting of the American Medical Association.

Members are urged to make reservations immediately, inasmuch as the hotels expect to be filled to capacity. Make your reservations directly with Chalfonte-Haddon Hall, advising them of the accommodations you wish. Rates are as follows:

	Chalfonte	Haddon Hall
Single room with bath:	$6, $7, $9	$7, $8, $10
Double room with bath (without ocean view):	$8 and $10	$10 and $12
Double room with bath (side ocean view):	$12	$14
Double room with bath (ocean front):	$14 and $16	$16 and $18

Make your reservations now and avoid disappointment—remember, you can always cancel them at a later date.

Those wishing to present papers should send the title of the paper and four copies of a comprehensive abstract to the president, Dr. Fuller Albright, Massachusetts General Hospital, Boston, Massachusetts, at their

earliest convenience. Abstracts submitted should be in proper form for printing in the program. Not more than the first two hundred words can be included in the printed abstract.

Further information regarding the meeting will be forthcoming at an early date.

The Francis Amory Septennial Prize of the American Academy of Arts and Sciences

In compliance with the terms of a gift under the will of the late Francis Amory of Beverly, Massachusetts, the American Academy of Arts and Sciences offers a substantial prize for outstanding work related to the alleviation or cure of diseases affecting human reproductive organs. The gift provides a fund, the income of which may be awarded at seven-year intervals "as a prize and gold medal, or other token of honor or merit," to any individual or individuals for work of "extraordinary or exceptional merit" in this field. In case there has appeared work of a quality to warrant it, the next award will be made in 1947. Awards will be made for what, in the judgment of the Committee on the Amory Fund, appears to be the most outstanding contribution or contributions in the field as outlined and as based on published work and recognized accomplishment for the current seven-year period.

No formal applications and no essays or treatises from individuals are solicited, but suggestions will be welcomed from any appropriate source that will be of aid to the Committee in making a wise selection.

Recommendations may be addressed to the Secretary, Amory Fund Committee, American Academy of Arts and Sciences, 28 Newbury Street Boston, Massachusetts.

National Research Council Grants for Research in Endocrinology

The Committee on Research in Endocrinology, National Research Council, wishes to announce that requests for grants-in-aid during the fiscal period from July 1, 1947, to June 30, 1948, will be received until February 28, 1947. Application blanks may be obtained by addressing the Secretary, Division of Medical Sciences, National Research Council, 2101 Constitution Avenue, Washington 25, D. C. In addition to a statement of the problem and research plan or program, the Committee desires information regarding the proposed method of attack, the institutional support of the investigation, and the uses to be made of the sum requested. No part of any grant may be used by the recipient institution for administrative expenses.

The Committee makes grants-in-aid of research in the general field of experimental and clinical endocrinology. However, applications for support of research in the problems of sex in the narrower sense cannot be given favorable consideration, and investigators seeking support in this field should direct their proposals to the Committee for Research in Problems of Sex of the National Research Council. The Committee on Research in Endocrinology, however, will continue to give consideration to the support of studies of the effect of sex hormones on nonsexual functions, e.g., on general metabolism and on the metabolism of steroid hormones.

Abstracts of

CURRENT ENDOCRINE LITERATURE

ADRENALS

BROSTER, L. R. AND GARDINER-HILL, H. A case of Addison's disease successfully treated by a graft. *Brit. Med. J.* 570 (1946).

A case is described in which a hypertrophied adrenal gland from a patient suffering from the adrenogenital syndrome was grafted by vascular anastomosis into a patient suffering with Addison's disease. Sodium chloride withdrawal tests showed a considerable amount of improvement after the operation, there being no longer any fall in blood sodium or blood pressure. At the time of this report, 14 months after operation, the patient had been without substitution therapy for seven weeks and had shown no symptoms of adrenal insufficiency.—*L.T.S.*

DEANE, H. W. AND GREEP, R. O. A morphological and histochemical study of the rat's adrenal cortex after hypophysectomy, with comments on the liver. *Am. Jour. Anat. 79:* 117–145 (1946).

Following hypophysectomy an extensive atrophy of the zona fasciculata of the adrenal cortex was observed, accompanied by a loss of ketosteroids as demonstrated by histochemical technics, and cytological changes suggestive of reduced secretory activity. In contrast, an actual thickening of the zona glomerulosa was reported with retention of ketosteroids and normal cytological structure. Liver glycogen was markedly reduced. Since hypophysectomy destroys the capacity of the adrenal cortex to regulate carbohydrate metabolism but does not seriously disturb its control over electrolyte metabolism, these findings were interpreted to support the theory previously advanced by others which postulates that the carbohydrate-regulating principles are secreted by the zona fasciculata and the salt-regulating substances by the zona glomerulosa.—*B.L.B.*

GREENE, R. F., PATERSON, A. S. AND PILE, G. C. L. Hypertrichosis with mental changes; effect of adrenalectomy. *Brit. M. J. 1:* 698 (1945).

Greene and his associates report the case of a woman, aged 25, who had hypertrichosis associated with mental changes which gradually resolved after adrenalectomy. The psychologic changes preceded the external physical changes. When first seen, she was drifting into a tense hypochondriacal state. The removal of most of the causes of her

anxiety did not bring about her recovery. Only after operation did recovery set in.—*Abst., Arch. Neurol. & Psychiat.*

ENDOCRINE GENERAL

ANDERSON, E. AND HAYMAKER, W. Cushing's syndrome. *J. Nerv. & Ment. Dis. 99:* 511 (1944).

Anderson and Haymaker review the controversy as to the pituitary or the adrenocortical origin of Cushing's syndrome. They believe that the demonstration of a substance resembling the hormone of the adrenal cortex in the blood and urine of patients with the disease is evidence of its adrenocortical nature. They report seven cases of the syndrome. In four cases death ensued, and in three cases improvement was observed. The occasional cyclic nature of the disease is illustrated in two of the cases, in which spontaneous remission occurred. In two cases the hair of the scalp changed from blond to black, and in one case became coarse. Studies of blood electrolytes revealed that the levels of potassium and sodium in the serum varied from time to time in the same patient, but in some of the cases the serum potassium tended to be at the lower range of normal. This observation may possibly be considered significant as an expression of an excess of adrenocortical hormone. In two cases significant amounts of adrenocortical hormone were found in the blood and urine, and in another case the hormone was demonstrated in the urine alone. The adiposity and hypertension which invariably occur with Cushing's syndrome may be due to the effects of the hormone of the adrenal cortex rather than of the androgenic fraction. Albright designated the former as the S hormone and the latter as the N hormone.—*Abst., Arch. Neurol. & Psychiat.*

FREEMAN, H. Resistance to insulin in mentally disturbed soldiers. *Arch. Neurol. & Psychiat. 56:* 74–78 (1946).

A study of the sensitivity of the blood sugar response to injected insulin in a series of 20 normal men and of 93 mentally disturbed soldiers revealed that the mean maximum level of hypoglycemia (in 30 minutes) was 29.6 mg. per 100 cc. in the former and 41.4 mg. in the latter. This difference in reactivity was statistically significant. Forty-six per cent of the patients showed a less pronounced drop in blood sugar than any of the normal subjects. The secondary rise in blood sugar following the hypoglycemia was the same in the two groups. This resistiveness to insulin was noted with all clinical types of mental disturbance and is probably indicative of a coincidental change in the reactivity of the endocrine factors controlling the regulation of blood sugar.—*Author's Summary.*

GODLOWSKI, Z. Insulin shock treatment of bronchial asthma. *Brit. M. J. 1:* 717 (1946).

A series of eight allergic and three nonallergic cases of severe bronchial asthma were treated with insulin shock. Seven of the eight asthmas classed as allergic have been permanently relieved. The time elapsed varied from ten months to two and one-half years. One case relapsed after five months. None of the three nonallergic cases was relieved by the insulin treatment. The classification of allergic was based on local findings typical of an allergic state and uniformly increased eosinophilia. In the allergic cases this dropped significantly in all cases except the one which relapsed.—*L.T.S.*

STUART, H. C. Normal growth and development during adolescence (concluded). *New Eng. J. Med. 234:* 732 (1946).

A general review of growth and development through adolescence is given. The sequence in the development of the secondary sex characteristics in both sexes, the relation of the menarche and menstruation to general growth and osseous development, and the changes in basal metabolism, calcium, and nitrogen retention, and the endocrine glands are discussed.—*L.T.S.*

GONADS

BARTON, M. AND WIESNER, B. P. The receptivity of cervical mucus to spermatozoa. *Brit. Med. J.* 606 (1946).

The authors report that semen and cervical mucus are virtually immiscible. Fecundation depends on the ability of the sperms to penetrate the interface between mucus and semen. The mode of invasion is described.

This process can be studied individually in special contact preparations, the receptivity of the mucus being assessed by exposure to fecund semen, while the semen is assayed against normal ovulatory mucus.

In many sterile women the mucus does not admit or sustain spermatozoa, and these findings are closely correlated with the results of Sims (postcoital) tests.

The nonsurgical treatment of cervical dysfunction is briefly surveyed with special reference to sulfonamides.—*L.T.S.*

CHARLES, A. H. A case of hydatidiform mole at age 52. *Brit. Med. J.* 460 (1946).

The author reports the case of a woman 52 years old in which a uterine mass, first diagnosed as carcinoma, was found to be a typical hydatidiform mole. No complications followed complete hysterectomy.—*L.T.S.*

COX, H. T. Treatment of carcinoma of the prostate by periurethral resection and stilbestrol. *Brit. Med. J.* 191 (1946).

The author discusses the results in a series of 30 consecutive cases of late carcinoma of the prostate during the past four years. It was found that extensive periurethral resection of the prostate was advisable where there was interference with micturition. Where urine excretion was not interfered with, periurethral resection of portions of the tumor was done for classification of the malignancy. The grading of the malignancy was found to be important both in judging survival and in regulation of estrogen dosage. Doses of 30 mg. of stilbestrol daily were used at the beginning of treatment. In the most malignant group it was found to be wise to increase this dose if relief was not adequate and never to lower it. In those with group 2 (Muir) malignancy it was also found wise not to lower the dosage. In group 1 malignancies it was found safe, subject to repeated examination, to lower dosage. The author feels that the failures with estrogenic therapy have been due to too small doses.

The most obvious effect of the estrogen therapy was the dramatic relief of pain. Known metastases when present at the beginning of treatment have showed slow but steady extension. Only one case, however, without initial bone metastases had developed any during treatment. The majority of cases showed a varying degree of prostatic softening after some weeks' treatment.

Stilbestrol showed some toxic reactions which were relieved when the patients were transferred to dienoestrol.—*L.T.S.*

DRILLEN, C. M. A study of normal and abnormal menstrual function in the auxiliary territorial service. *J. Obst. & Gynaec. Brit. Emp. 53.* (3): 228 (1946).

The author interviewed over 700 recruits and serving auxiliaries in order to obtain data on menstrual function in young women and the influence of service on that function. Nearly 50 per cent had no symptoms at menstruation. Dysmenorrhea was most commonly seen in girls in their early twenties and was aggravated by anxiety. Irregularity was also highest in the early twenties. Amenorrhea was less frequent among officers.—*R.A.C.*

MILTON, R. F. The xenopus pregnancy test. *Brit. Med. J.* 328 (1946).

The author gives a brief historical account of the test, together with the details, of the chromatographic concentration of gonadotropic substance as introduced by Hogben, *et al.* He concludes with the statement that this technic will give a positive result with 500 I.U. per day and that, in his hands, the test has been extremely satisfactory.—*L.T.S.*

PARRELLA, D. Further observations on prostigmine in delayed menstruation and pregnancy. *West. J., Surg., Obst. and Gyn. 54:* 397–402 (1946).

The response of 200 patients with delayed menstruation to a series of injections of prostigmine is reported. Only those women who had had a normal menstrual history prior to the present complaint, who were not within the usual menopausal age, and in whom endocrine dysfunction and organic pelvic pathology had been ruled out, were incorporated in the series. The injection of prostigmine was followed by the onset of uterine bleeding in 77 instances. A provisional diagnosis of pregnancy was made in the 138 cases in whom prostigmine did not induce menstrual flow. Confirmation of the diagnosis of pregnancy was obtained in 137 instances. The one false positive case had a negative Friedman test and on closer inquiry proved to have manifestations of an early menopausal syndrome. In eight instances of pregnancy, the prostigmine test was positive whereas the Friedman test was negative; in three instances, false negative Friedman tests which later became positive had been preceded by positive prostigmine tests. Prostigmine had no adverse effects upon the state of gravidity.—*J.M.*

ROBBINS, S. L., PARKER, F., JR. AND DOYLE, W. C. The use of the South African frog (xenopus laevis) in the diagnosis of pregnancy. *New Eng. J. of Med. 234:* 784 (1946).

A series of 100 urine samples was assayed by both the South African frog test and the immature rat test of Aschheim and Zondek. There were no false positive reactions in either case, but there were four false negatives with the frog test when the original procedure using 40 cc. of urine was followed. The procedure was modified by using 80 cc. of urine and observing the frogs 48 hours after injection instead of 24. The advantages of the frog test are that it is more rapid, the test being positive, in most cases, in 8 to 24 hours; the frogs can be used repeatedly over a long period; and the surgical technic is eliminated in determining the results of the test. The disadvantages are the need of

concentrating the urine by precipitation and a somewhat lower sensitivity if the original technic is used. If, however, the minor modifications suggested by the authors are used, they believe that the sensitivity compares favorably with the older tests.—*L.T.S.*

SCHNEIDER, C. L. A toxic principle from progestational endometrium and placenta. *Proc. Soc. Exp. Biol. and Med. 62* (2): 322–325 (1946).

Saline extracts of different portions of the uterus in various functional states and of the liver, intestine, and skeletal muscle of several species (among them the human, cow, sheep, rabbit, rat, and mouse) were made. The toxicity of the extracts was tested in young white mice and the results measured as the number of minimum lethal doses or "units" per cc. The most toxic extracts were obtained from preparations which contained endometrium or placenta, and endometrium under progesterone influence was more toxic than that in other physiologic states. Small amounts of material with a similar effect were present in skeletal muscle extracts. The exact nature of the toxic substance was not determined, but it appeared to have properties consistent with those of a protein. The author reported that the substance may be the same as that described as histamine-like by Krichesky and Pollock, and that it is doubtful if it is the same as the menstrual toxin of Schick or of Macht and Lubin.—*F.N.A.*

PANCREAS

MILLETT, JOSEPH AND DARBY, RICHARD T. Infectious diabetic gangrene of the skin of the neck. *New Eng. J. of Med. 235:* 12 (1946).

A case of extensive infectious diabetic gangrene of the skin involving the entire neck is reported. Treatment with penicillin was successful in controlling the infection. Adequate control of the diabetes led to healing of the lesion with no complete sloughing of the skin except in certain small areas. A differential diagnosis of the condition is considered which distinguishes it from erysipelas in the early stages and carbuncles in the later stages.—*L.T.S.*

PITUITARY

BECKS, H., SIMPSON, M. E., EVANS, H. M., RAY, R. D., LI, C. H. AND ASLING, C. W. Response to pituitary growth hormone and thyroxin of the tibias of hypophysectomized rats after long postoperative intervals. *Anat. Rec. 94:* 631–655 (1946).

The administration of a purified growth hormone preparation to hypophysectomized rats after postoperative intervals ranging from about 271–502 days, proved to be effective in eliciting osteogenesis in the atrophic epiphyseal cartilage of the tibia. Treatment with thyroxine alone caused some proliferation of the cartilage cells but induced little osteogenesis; when injected in nontoxic doses with growth hormone, it synergized the action of the latter substance. Thus it is evident that in spite of the prolonged absence of growth in the tibia, the growth mechanism can be reactivated by treatment with growth-promoting substances. Further, growth hormone caused a marked activation of some portions of the cartilage under the articulating surface of the epiphysis. In contrast to its effect on the tibia, thyroxine antagonized this action.—*B.L.B.*

DAWSON, A. B. Some evidences of specific secretory activity of the anterior pituitary gland of the cat. *Am. Jour. Anat. 78:* 347–410 (1946).

By special staining methods the author has been able to differentiate two types of acidophiles in the anterior hypophysis. The cells of one of these types have been designated as "carminophiles" because of their affinity for the carmine dye. The carminophiles were studied exhaustively in relation to various reproductive states with three cycles of elaboration and release of secretion by them being found: namely, a preovulatory, a preimplantation, and one extending from the middle of pregnancy to the close of lactation. Correlation of these periods of secretory activity with ovarian physiology strongly suggests that the carminophiles of the cat may be the source of lactogen (luteotropin) which controls the secretory activity of the corpus luteum.—*B.L.B.*

DONIACH, I. AND WALKER, A. H. C. Combined anterior pituitary necrosis and bilateral necrosis of the kidneys, following concealed accidental hemorrhage. *J. Obst. & Gynaec. Brit. Emp. 53.* (2): 140–147 (1946).

This article describes a case in which concealed accidental hemorrhage was followed by both pituitary and renal necrosis. The patient, a white married woman aged 31, para 2, was admitted after five hours of severe, constant, abdominal pain two months before the expected date of delivery. There had been some edema of the feet three days prior to admission which extended two-thirds of the way up to the knees on admission. She was then pale and cold, but the B.P. was 150/80. There was slight vaginal bleeding. The fundi were normal, the hemoglobin 5 g. per cent. Two pints of Group O 4 blood were given. Her blood group was A 2 Rh negative, and she had no anti-Rh agglutinins in her serum (tested seven days later). The husband was group O 4, Rh positive. A fresh, stillborn fetus was delivered shortly after admission, and 26 ounces of old and fresh clot expressed after the placenta. One-half ounce of urine obtained by catheter contained 750 mg. per cent of albumin. Only a few ounces of urine were excreted in the next week, edema increased, the blood potassium and urea levels rose. She died on the seventh day. The anterior pituitary showed massive coagulative necrosis and thrombosis of the veins but not of the arteries of the pituitary stalk. The cortex and columns of Bertini of the kidney showed widespread ischemic coagulative necrosis attributed to stasis and thrombosis in the interlobular arteries. Centrilobular focal necroses were found in the liver. The literature is reviewed and the mechanism of the circulatory disturbances leading to the pathological changes discussed.—*R.A.C.*

MELTON, E. I. AND MCNAMARA, W. L. Hodgkin's disease involving the pituitary gland with diabetes insipidus. *Ann. Int. Med. 25:* 525–531 (1946).

A case of diabetes insipidus, proved at autopsy to be due to Hodgkin's disease which destroyed the posterior lobe of the hypophysis, is reported.—*J.M.*

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† Abstract of paper presented at the Twenty-eighth Annual Meeting of The Association for the Study of Internal Secretions.

Other items are abstracts of articles which appeared in current medical journals.

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